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Appendix I: Deleted appendix documents: NICE short clinical guideline 87 – Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes

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Draft for Consultation

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Part 1. 6.2 Appendix I2 – Technology assessment report

Newer agents for blood glucose control in type 2 diabetes

A health technology assessment commissioned by the UK Health Technology Assessment Programme in support of the NICE Short Clinical Guidelines Programme.
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About the Aberdeen HTA Group

The Aberdeen Health Technology Assessment Group is part of the Institute of Applied Health Sciences (IAHS), which is part of the College of Medicine and Life Sciences of the University of Aberdeen. The Institute of Applied Health Sciences is made up of discrete but methodologically related research groups. The HTA Group is drawn mainly from the Health Services Research Unit, the Department of Public Health, and the Health Economics Research Unit.

The HTA Group carries out independent health technology assessments, producing technology assessment reports (TARs) for the UK HTA Programme, which commissions TARs for NICE and other bodies, such as the National Screening Committee. The group has produced previous TARs on diabetic topics, including;

Continuous subcutaneous insulin infusions (insulin pumps)
Screening for type 2 diabetes
Prevention of diabetes by non-pharmacological interventions in people with impaired glucose regulation
Inhaled insulin

We also do Cochrane reviews on diabetes topics.

About the Cochrane Metabolic and Endocrine Disorders Review group

The Cochrane Metabolic and Endocrine Disorders Group (CMED) is one of the collaborative review groups of the Cochrane Collaboration. It is primarily concerned with the evaluation of health care interventions for the prevention, treatment or management, and rehabilitation of metabolic, nutritional and endocrine disorders, such as diabetes.

The CMED Group aims to serve several groups of people, including;

- Health care workers – by providing high quality, regularly updated and easily accessible summaries of scientific knowledge
- Patients (present and potential) and relatives – directly by providing them with high quality information; indirectly by supporting health care workers and policy-makers
- Researchers and those who commission research – by accurately summarising present knowledge identifying research gaps; also through development of methodology for systematic reviewing
- Policy-makers – by producing accessible and reliable summaries, free of the biases which may be present in submissions by groups with a particular interest. Support to poicy-makers may be indirect, via support to those who produce policy analyses for governments and others, such as health technology assessment units
- Undergraduate and postgraduate students – through the provision of concise reviews of difficult topics.

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Abbreviations

ADA	American Diabetes Association
BMI	body mass index
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CHF	chronic heart failure
CI	confidence intervals
CORE	Center for Outcomes Research,
CSII	continuous subcutaneous insulin infusion
CV	cardiovascular
DAFNE	Dose Adjustment For Normal Eating
DAWN	Diabetes Attitude Wishes and Need
DCCT	Diabetes Control and Complications Trial
DPP-4	dipeptidyl peptidase-4
DSC-R	Diabetes Symptom Checklist-Revised
EASD	European Association for the Study of Diabetes
EMEA	European Medicines Evaluation Agency
EQ-5D	EuroQol
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GDG	Guideline Development Group
GLP-1	glucagon-like peptide-1
HDL	high density lipoprotein
HFS	Hypoglycaemia Fear Survey

ADA	American Diabetes Association
HR	hazard ratio
HOMA-beta	homeostasis model assessment beta
ICER	incremental cost-effectiveness ratio
IDF	International Diabetes Federation
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IHD	ischaemic heart disease
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
ITT	intention to treat
IU	International Unit
LDL	low density lipoprotein
MDI	multiple daily injections
MHRA	Medicines and Healthcare Produces Regulatory Agency
MI	myocardial infarction
MTRAC	The Midlands Therapeutics Reviews and Advisory Committee
NPH	Neutral Protamine Hagedorn
OGLA	oral glucose lowering agents
OR	odds ratio
PG	plasma glucose
PGWB	Psychological General Well-Being Index
PPAR-g	peroxisome proliferator-activated receptor-g
PSSRU	Personal Social Services Research Unit.
QALY	quality adjusted life year
QoL	quality of life
RCPE	Royal College of Physicians of Edinburgh
RCT	randomised controlled trial
SMC	Scottish Medicines Consortium
TA	Technology Assessment
TFS	Treatment Flexibility Scale
TZD	thiazolidinediones
UKPDS	United Kingdom Prospective Diabetes Study
UTI	urinary tract infection
VAS	visual analogue scale
WMD	weighted mean difference
YHPHO	York and Humber Public Health Observatory

Summary

Background

NICE issued an updated guideline (Clinical Guideline 66) for the management of all aspects of type 2 diabetes in May 2008. However new drug developments means that this guideline itself already requires an update. This technology assessment report aims to provide information to support the Short Guideline Development Group (GDG) which will produce a "new drugs update" to the 2008 guideline.

The four classes of drugs which the GDG have been asked to consider are;

- The glucagon-like peptide 1 analogue, exenatide, in its currently available form, given by injection twice daily. The second drug in that class, liraglutide, was not licensed in time to be included in the guideline update, and nor was the long-acting form of exenatide.
- The dipeptidyl peptidase 4 inhibitors, sitagliptin and vildagliptin
- The long-acting insulin analogues, glargine and detemir. Glargine had been the subject of a previous technology appraisal (TA 43) but it was felt that this needed updated. Detemir had not previously been appraised by NICE.
- The thiazolidinediones (hereafter referred to as the glitazones), more from the safety aspects than for glycaemic control.

Methods

Systematic review of clinical effectiveness studies (systematic reviews and new trials) and economic evaluations.

The bibliographic databases searched were MEDLINE 1990- April 2008, Embase 1990 – April 2008, the Cochrane Library (all sections) Issue 2, 2008, and the Science Citation Index and ISI Proceedings (2000 – April 2008). The websites of the American Diabetes Association, the European Association for the Study of Diabetes, the US Food and Drug Administration, the European Medicines Agency (EMEA) and the Medicines and Healthcare Products Regulatory Agency were searched, as were manufacturers' websites. References cited by retrieved studies were checked for other trials. Auto-Alerts were set up so that new studies were identified as they appeared. For the review of the DPP-4 inhibitors, we searched only for studies published since the time of the searches for the very recent Cochrane review, and used data from that review.

Abstracts of retrieved studies were checked for relevant studies by two reviewers, and in cases where there was doubt, copies of full papers were obtained. Only English language studies were obtained.

Data extraction was carried out by one person, and checked by a second, using pre-defined tables. Studies were assessed for quality using standard methods for reviews of trials as appropriate.

Meta-analyses were done using the Cochrane Review Manager software.

Inclusion and exclusion criteria were based on current standard clinical practice in the UK, as outlined in NICE Clinical Guideline 66. This meant that only studies of the new drugs versus an appropriate comparator, and in an appropriate situation, were used. It was assumed that treatment of type 2 diabetes would start with lifestyle measures, principally diet, followed by metformin monotherapy, then by the addition of a sulphonylurea. So the new drugs would be used in addition to metformin and sulphonylurea combination treatment, or as second-line therapy, particularly in those unable to tolerate adequate doses of those drugs. The main implication of this was that trials of the new drugs versus placebo, or as first-line

monotherapy, or comparators not relevant to standard practice as laid down in CG 66, were excluded.

The outcomes of most interest for the GLP-1 analogues, DPP-4 inhibitors and the long-acting insulin analogues were;

- Glycaemic control, as reflected by HbA1c, and taken to be an indicator of the risk of long-term complications of diabetes
- Hypoglycaemic episodes
- Changes in weight
- Adverse events
- Quality of life
- Costs

We did not expect to find any trials long enough to have microvascular or macrovascular events as endpoints.

For the glitazones, the main interest was safety, especially the risk of cardiovascular events.

Cost-effectiveness analysis

Modelling of the cost effectiveness of the various regimes has used the UKPDS Outcomes Model, which models the first occurrence of a variety of downstream complications of diabetes and estimates the cost and quality of life impact of these. This was undertaken first for a representative male patient of BMI 30kg/m2 who was assumed to be reaching the 7.5% HbA1c intensification threshold, but was repeated for males with BMI 35, and for females with BMIs 30 and 35.

The absolute HbA1c impacts, weight impacts, cholesterol impacts and SBP impacts for the head to head comparisons as identified within the clinical effectiveness section were applied as 1st line treatment and the UKPDS Outcomes Model given an initial run to predict the evolution of HbA1c. Since treatment would be intensified again once the 7.5% HbA1c intensification threshold was reached; e.g. intensification from 1st line oral treatment to 2nd line basal insulin at the point the UKPDS Outcomes Model predicted the HbA1c would rise above 7.5%, the effectiveness of the 2nd line treatment was applied. The UKPDS Outcomes Model was run a second time to predict the sawtooth evolution of HbA1c for this 1st line, 2nd line combination treatments. In a like manner, where a 3rd line intensification was possible; i.e. switching from 2nd line basal insulin to 3rd line basal bolus insulin, the procedure was undertaken once more with the assumption of a 0.5% improvement in HbA1c on the switch to 3rd line basal bolus insulin.

Costs took into account the need for education and support on starting insulin, and the need for home blood glucose testing. This contrasts with exenatide which has a fixed dose. The UKPDS Outcomes Model predicted the total cost and QALYs arising from routine care and the microvascular and macrovascular complications of diabetes for each treatment sequence.

However, while the UKPDS Outcomes Model is well validated, it does not directly address aspects of the treatments under consideration: e.g. the direct utility effects from weight loss or weight gain, severe hypoglycaemic events, and the fear of severe hypoglycaemic events. As a consequence, the survival curves of the UKPDS Outcomes Model were used to append these effects to the cost and QALY estimates of the UKPDS Outcomes Model.

Results – clinical effectiveness

The GLP-1 analogue - exenatide

We looked first for trials in which exenatide was added to dual therapy with metformin and sulphonylurea, when that combination failed to achieve adequate glycaemia control. Comparators could be placebo, or a glitazone, or insulin.

There were five randomised controlled trials of reasonable quality which addressed our main questions. The main quality problems were insufficient reporting of methods (such as how randomisation was done) and lack of optimisation of other treatments (such as insulin dose). One trial was of exenatide versus insulin in people who were already on insulin. We added two other trials which did not meet our original criteria. One was added in order to provide more data on the insulin versus exenatide comparison; it was in patients who had failed only monotherapy with metformin. The other compared metformin monotherapy with metformin plus exenatide, and was added at the request of the NICE Guideline Development Group to address the question of how to treat patients whose weight was of considerable concern, and in whom adding a sulphonylurea or a glitazone would cause undesirable further weight gain. All trials were sponsored by, and/or had co-authors from, the manufacturer.

HbA1c

In patients with inadequate control on two oral glucose lowering agents, the addition of exenatide led to a fall in HbA1c of about 1%.

In trials against insulins, results on HbA1c were comparable. In one trial in which insulin glargine or exenatide were added to the metformin and sulphonylurea combination, HbA1c was reduced by 1.1% in both groups. In the trial in which exenatide or glargine were added when metformin monotherapy failed, both groups had a reduction of almost 1.4% in HbA1c.

Hypoglycaemia

Severe hypoglycaemic events were few in the trials. With oral combinations, most hypoglycaemic events seen with exenatide were when it was used in combination with a sulphonylurea.

Compared to insulin, there was less nocturnal hypoglycaemia with exenatide, but differences were not marked.

Weight

When exenatide is added to dual therapy, patients tend to lose weight – on average about 2 kg. In comparisons with insulin, patients on exenatide lost weight whereas those on insulin tended to gain it, giving a difference which can be of the order of 5 kg.

Adverse effects

About half the patients on exenatide suffer from nausea. This is usually more at the start of treatment, and is usually moderate or mild. Vomiting is quite common. In the trials, only a small proportion had to stop exenatide because of nausea. In some observational studies, there were higher cessation rates. It is worth noting that the weight loss is not due only to nausea.

Issues

At present, exenatide has to be given by injection, twice daily. A long-acting form is under development which can be given once-weekly. It has been suggested, based on animal experiments, that the GLP-1 agonists may preserve beta cell function. This is unproven in humans. Some studies show that the effect of exenatide wears off after it has been stopped, suggesting that there is no significant effect on beta cell capacity.

Cases of pancreatitis have been reported in people taking exenatide. Most of the early reports were in people with other possible causes of pancreatitis, but with more cases being reported, it looks as if pancreatitis may be a real but rare side-effect of exenatide treatment. The FDA and the MHRA have asked for heightened vigilance and reporting, but have not suggested that exenatide should not be used. If the link is confirmed, the balance of risks between occasional pancreatitis and poorly controlled diabetes will need to be considered.

Summary on exenatide

Exenatide is effective in improving glycaemic control by 1% or a little more, and has the added benefit of modest but useful weight loss. The downside is that it causes frequent nausea (although usually not major and tending to wear off with time), that it has to be given by (at present) twice daily injections, and that there may be a small risk of pancreatitis.

The DPP-4 inhibitors (gliptins)

The licences for these drugs at the time of the review were only for dual therapy with metformin, a glitazone, or (vildagliptin only) a sulphonylurea. However we thought that triple therapy with a metformin, sulphonylurea and a gliptin would be a logical use of the drugs, and looked for trials of that as well. We also looked for trials in which a gliptin was used in combination therapy as an alternative to adding insulin to (usually) metformin.

Only four published trials met our inclusion criteria. All were sponsored by, and had co-authors from, the manufacturers. Two compared a gliptin plus metformin with a glitazone plus metformin. One examined the effect of adding sitagliptin to dual therapy with metformin and sulphonylurea (glimepiride or glipizide). The fourth took patients failing on metformin and added a gliptin or glipizide.

HbA1c

In combination with metformin, the gliptins reduced HbA1c by similar amounts (about 0 .8%) to a glitazone. When added to dual therapy with metformin and glimepiride, sitagliptin reduced HbA1c by about 0.8% compared to the placebo group. When compared to glipizide in dual therapy with metformin, both reduced HbA1c by 0.7%. Reductions are higher in those whose baseline HbA1c is higher, for example a drop of 1.3% in those with baseline HbA1c over 9%.

Hypoglycaemia

No severe hypoglycaemic episodes were reported in patients in the trials. In the wider Cochrane review, severe hypoglycaemia was not reported in any patient on sitagliptin or vildagliptin. Hypoglycaemia was rare in the dual therapy combinations.

Weight

The DPP-4 inhibitors did not seem to have the same weight loss effect as exenatide. In the trials against glitazones, there was less weight gain in the DPP-4 groups, but that reflected weight gain on glitazones rather than loss on a DPP-4 inhibitor. However, absence of significant weight gain is a useful benefit, compared to sulphonylureas and glitazones.

Adverse events

In the short term, the gliptins were very well tolerated. Nausea was not increased. Longer-term data are needed to ensure that there are no adverse effects mediated by the immune system. Data from the Cochrane review show a statistically significant increase in infections with sitagliptin (relative risk 1.29; 95% CI 1.1 – 1.5, p = 0.003) but not with vildagliptin (RR 1.04; 95% CI 0.87 – 1.24).

Other studies.

The Cochrane review found 29 comparisons from 25 trials, most of which did not meet our inclusion criteria, usually because they were of gliptin monotherapy versus placebo, or against metformin monotherapy. However these trials suggest that compared to placebo, the gliptins reduce Hba1c by 0.6-0.7%. When compared to monotherapy with other agents, neither drug showed any advantage in HbA1c.

Summary

The gliptins are effective in glycaemia control, reducing HbA1c by about 0.8% in the included trials. Hypoglycaemia was not a problem, and nor was weight gain. Data are required on long-term safety.

Exenatide versus the gliptins.

There are no published head to head trials comparing exenatide with either of the gliptins. The main differences are that the DPP-4 inhibitors are given orally, are less expensive, cause fewer side-effects in the short-term, and are weight –neutral rather than having the weight loss seen with exenatide. They may be a little less potent in lowering HbA1c, but that impression is based on indirect comparison, and should be treated with caution.

Long-acting insulin analogues

Given the number of previous reviews, we started by identifying good quality systematic reviews, and then looked for new trials published since the reviews. We drew on three good quality reviews, which included 14 trials of glargine and two of detemir. Three new trials were found, one of glargine and two of detemir. We combined the new trials with the relevant older ones in updated meta-analyses. We also noted one trial of glargine versus detemir.

HbA1c.

There was no difference in HbA1c between glargine and NPH, and only a small but non-significant difference in trials of detemir versus NPH (HbA1c was higher with detemir by 0.08%; 95% CI – 0.03 to + 0.19).

Hypoglycaemia.

There were no differences in the frequency of severe hypoglycaemia between the analogues and NPH, but overall hypoglycaemia was less frequent with both glargine (OR 0.74; [95% CI: 0.63 to 0.89]) and detemir (OR 0.51 [95% CI 0.35 to 0.76]). Many of the hypoglycaemic episodes were nocturnal, and the odds ratios for those were 0.47 (95% CI: 0.37, 0.59) for glargine and 0.48 (95% CI: 0.37, 0.63) for detemir.

Weight.

The meta-analyses showed that those on glargine gained slightly less weight than those on NPH (0.28kg; 95% CI -0.72 to + 0.15) but this was neither clinically nor statistically significant. On detemir, the difference was a little greater (1.2kg; 95% CI -1.6 to – 0.8kg). In the head to head trial of glargine versus detemir, those on glargine gained 3.5kg on average, compared to a gain of 2.7kg on detemir, but the difference of 0.8kg is of doubtful clinical significance. The difference applied only to those on once daily detemir; those on two injections daily gained 3.7 kg.

Insulin dose.

In the head to head trial, the mean daily dose was higher for detemir (0.52 units/kg with once daily injections; 1.0 units/kg with twice daily) than for glargine (0.44units /kg with once daily).

Summary

Glargine and detemir are equivalent to NPH (and to each other) in terms of glycaemic control as reflected in HbA1c, but have modest advantages in terms of hypoglycaemia, especially nocturnal. There is little to choose between the two analogues. Detemir when used once daily only, appears to have slightly less weight gain than glargine, but the difference in the head to head trial was under 1 kg and is probably not clinically significant and detemir requires a slightly larger daily dose, at higher cost with present prices.

The glitazones

Little new has emerged since the last guideline was produced. Pioglitazone and rosiglitazone appear to have similar effectiveness in controlling hyperglycaemia, and similar toxicity in terms of oedema, heart failure and fractures (in women only). However the current evidence suggests that rosiglitazone increases the risk of heart attacks and cardiovascular mortality but that pioglitazone reduces it. The statistical significance of the increased risk for rosiglitazone is still debated. Most analyses show an increase in relative risk but some find that this is not statistically significant. This is partly because in most of the trials, the absolute risk of cardiovascular events was low. Most trials were short-term with HbA1c as the main outcome.

Most of the regulatory and prescribing advisory bodies have asked for warnings on rosiglitazone but have allowed its continued use. Some have suggested that in future, pioglitazone be used in preference. Recent prescribing data from the USA shows a marked drop in the use of rosiglitazone, but suggest a shift to gliptins rather than a straight switch to pioglitazone.

Pioglitazone added to insulin

Pioglitazone is licensed for use with insulin when metformin is contraindicated or not tolerated. We included eight trials that examined the benefits of adding pioglitazone to an insulin regimen. In our meta-analysis, the mean reduction in HbA1c was 0.5% (95% CI: -0.73 to – 0.28). Hypoglycaemia was more frequent in the pioglitazone arms (relative risk 1.30; [95% CI: 1.04 to 1.63]). In most studies, those on pioglitazone gained more weight than those who were not, with an average difference of almost 3kg.

Results - costs and cost-effectiveness

The comparisons below are based on evidence from trials of direct comparisons, and so we are limited in what can be done. Costs were changing during the review. The analysis was bedevilled by very small differences in QALYs amongst the drugs, leading to fluctuations in ICERs even with 250,000 iterations.

All costs given here will almost certainly be out of date by publication time.

In terms of annual acquisition costs, among the non-insulin regimes for a representative patient with a BMI of around 30kg/m2 the gliptins are the cheapest of the new drugs with costs of between £386 and £460. The glitazone costs are similar with a total annual cost for pioglitazone of around £437 and for rosiglitazone of around £482 (though this is expected to fall shortly), though this situation may change as they come off patent and generic varieties become available. Exenatide is somewhat more expensive, with an annual cost of around £830. Regimens containing insulin fall between the gliptins and exenatide in terms of their direct costs (including all costs), with NPH-based regimen having an annual cost of around £468 for the representative patient while the glargine and detemir ones are considerably more expensive at around £634 and £716 respectively. Also, insulin dose increases with patient weight and for a BMI of 35 the annual cost of the NPH regime rises to £576, while the cost of glargine rises to £806.

But it should be noted that this is for an insulin regime containing only basal insulin. As beta cell function declines and control worsens, mealtime insulin will be required, increasing annual costs, for example, to around £617 for NPH and £783 for glargine for the representative patient with BMI of 30kg/m2.

For the comparison of exenatide with glargine it is anticipated that the net lifetime cost difference will be between a little over £1,000 more costly with exenatide. (NB it is assumed that patients will only stay on exenatide for a few years before insulin is required because of disease progression.) Given an anticipated QALY gain of around 0.057, this results in an estimated cost effectiveness of around £20,000 per QALY. This improves to a cost effectiveness estimate of around £1,600 per QALY for a patient with a BMI of 35kg/m2 due mainly to the increased cost of the glargine regime. The dose of glargine increases with weight, whereas that of exenatide is fixed. However, these cost effectiveness estimates are sensitive to the direct utility gain assumed for weight loss and weight gain, and if this effect is excluded the anticipated cost effectiveness of exenatide relative to glargine increases to between £9,000 per QALY and £21,000 per QALY, for the no-complications and with complications scenarios respectively. The term “direct utility gain” refers to the fact that people feel happier if they lose weight, and is in contrast to the indirect gain achieved when weight loss favourably affects variables such as cholesterol or blood pressure. The UKPDS model already allows for indirect gains from weight loss.

So what this analysis is telling us is that over a lifetime, there is little difference in costs of using exenatide for a few years instead of going straight to insulin; there is a slight benefit in QALY terms mostly due to the weight loss with exenatide. If patients did not lose sufficient weight, exenatide would not be cost-effective.

In summary, taking into account effects, side-effects, costs and expected time to progression, and assuming sufficient weight is lost, exenatide when compared to glargine appears to give ICERs within the range usually regarded as cost-effective. Provided that the effect of exenatide on BMI is reasonably consistent across the weight range, the cost-effectiveness of exenatide relative to glargine improves as BMI worsens, due in large part to the increasing cost of the required total glargine dose.

Comparing sitagliptin and rosiglitazone, the anticipated net QALY gain from sitagliptin is only 0.02 to 0.03 which is marginal and well within the bounds of error. However, sitagliptin is anticipated to be less expensive. If the direct utility effects of weight changes are excluded from this sitagliptin is associated with a very small utility loss of -0.006 QALYs though this does not affect the anticipated cost saving. Hence, the two drugs could be regarded as clinically equivalent but with sitagliptin marginally less costly at current prices.

For vildagliptin compared with pioglitazone the differences are again slight, with vildagliptin being associated with an insignificant QALY difference of between -0.011 and -0.007 QALYs. Hence the two drugs could be regarded as clinically equivalent, but vildagliptin is anticipated to be around £600 less expensive than pioglitazone (at current prices – a fall of 22% in the cost of pioglitazone would equalise costs).

In summary, the gliptins and the glitazones appear roughly equivalent in glycaemic effect, but the former have an advantage in avoidance of weight gain, which together with their lower (at present) costs gives them an edge. However, given the uncertainties around the ICER estimate, it would be inappropriate to say that the glitazones were definitely less cost-effective than the gliptins. The cost-effectiveness hangs heavily on the benefits of weight differentials.

This does not take into account the side-effects of the glitazones. Both have problems with fractures (in women only) and heart failure, but rosiglitazone also appears to increase the risk of cardiovascular disease. However, until we have longer follow-up we will not know whether the gliptins have as yet unreported side-effects.

For the comparison of glargine with NPH, the additional anticipated cost of around £1,800 is associated with an insignificant QALY gain: yielding cost effectiveness estimates of between £280,000 per QALY and £320,000 per QALY.

Within the comparison of detemir and NPH, the overall treatment costs from detemir are slightly higher being between £2,700 and £2,600. QALY gains are again slight – about 0.015 to 0.006. Cost per QALY range from £188,000 to £412,000.

Hence on cost-effectiveness grounds, NPH should be the first choice insulin in type 2 diabetes. However, some patients will have more trouble with hypoglycaemia than others, and will potentially have more to gain.

In summary, as in Clinical Guideline 66, NPH should be preferred as first line insulin, rather than a long-acting analogue. The analogues have modest advantages but at present much higher cost.

In some patients, the benefits of the analogues relative to NPH may be greater, and cost-effectiveness correspondingly better.

Discussion

The main weaknesses in the evidence base at present are;

- long-term data on the safety of exenatide and the gliptins
- a lack of trials directly comparing exenatide and the gliptins
- lack of data on the effects of exenatide and the gliptins on cardiovascular outcomes
- a lack of head to head trials of exenatide and NPH.

Research needs.

We need long-term follow-up studies of exenatide and the gliptins, although it is likely that exenatide will in future be used as the long-acting form, once weekly or even less often, and trials should use that form. Preliminary data from trials suggests that it will be more effective than the twice daily form.

Data on combined insulin and exenatide treatment would be useful. The combination appears logical, but practice appears to be running ahead of evidence.

In routine care, how much does compliance fall off as complexity of regimens increases?

More economic analysis is required, done independently of the manufacturers, including;

- When does it become cost-effective to switch from NPH to a long-acting analogue?
- The evidence for the direct utility of weight gain, or of avoiding weight loss, needs strengthened.

Conclusion

The new drugs, exenatide, the gliptins and (the not so new) detemir are all clinically effective.

The long-acting insulin analogues, glargine and detemir, have only slight clinical advantages over NPH, but have much higher costs, and hence very high ICERs. They are not cost-effective as first line insulin compared to NPH insulin in type 2 diabetes.

Exenatide, when used as third drug instead of progressing immediately to insulin therapy after failure of dual oral combination therapy, appears cost-effective relative to glargine, the current market leader, with most ICERs around £20,000, acceptable by current NICE standards. However exenatide would not be cost-effective compared to NPH.

The gliptins are comparable to the glitazones in glycaemic control and costs, but at present appear to have fewer long-term side-effects.

1 Chapter 1 Introduction

1.1 Type 2 diabetes

Diabetes mellitus is characterised by raised blood glucose levels. In non-diabetic people, the level of glucose in the blood is controlled by a balance of hormonal actions, principally insulin and glucagon, both of which are produced by specific types of cell in the pancreas, beta cells producing insulin, and alpha cells producing glucagon. Insulin lowers blood glucose and glucagon raises it. In type 1 diabetes, the beta cells are lost because of an auto-immune process, little or no insulin is produced, and insulin treatment is required for survival. The cause or causes of type 1 diabetes are not known.

Type 2 diabetes is usually seen in people who are overweight or obese, particularly if inactive. They are usually insulin resistant, and therefore require higher levels of insulin in order to keep blood glucose within the normal range. The pancreatic beta-cell is initially able to compensate for insulin resistance, by increasing production, thereby maintaining normal blood glucose levels. The higher than usual level of insulin is known as hyperinsulinaemia.

However, in most patients who may develop type 2 diabetes, the pancreatic beta-cell function progressively declines, leading to hyperglycaemia and clinical diabetes.[1] In the United Kingdom Prospective Diabetes Study (UKPDS), beta-cell function was found to be impaired at diagnosis, especially in patients who were not overweight.[2] Individuals with type 2 diabetes may have few or none of the classic clinical symptoms (such as thirst, passing abnormally large amounts of urine) of hyperglycaemia, and may be diagnosed incidentally, as seen in the UKPDS [3] where 33% were found by incidental means (for example, urine testing for an insurance medical) and 53% via symptoms.

The difficulty in maintaining metabolic control over time may be related to several behavioural factors (for example difficulties with healthy eating, exercise, medication regimens) but primarily reflects the underlying progressive decline in beta-cell function[4] , so that over a 9-year follow-up period, control deteriorated.[5]

Type 2 diabetes has traditionally been treated in a stepwise manner, starting with lifestyle modifications and encouragement of physical activity and when necessary, pharmacotherapy with oral agents (NICE guideline, published May 2008).[6] Several classes of oral agents are available. Until recently, these included;

- insulin secretagogues, which stimulate the pancreas to release more insulin, by binding to a sulphonylurea receptor. The main group is the sulphonylureas. There are seven of these in the British National Formulary (BNF), but older ones such as chlorpropamide are now little used. The ones most used in the UK are gliclazide, glipizide, glimepiride and glibenclamide (glyburide). A newer group of secretagogues is the meglitinide analogues, including nateglinide and repaglinide, but these are used far less than the sulphonylureas. They bind to the same receptor, but are less potent than the sulphonylureas.[7] They are shorter-acting, and have been suggested for controlling postprandial hyperglycaemia, perhaps in combination with a long-acting insulin.
- insulin sensitizers, which make tissues such as the liver and the muscles more sensitive to insulin (i.e. they reduce the insulin resistance). The commonest one in the UK is metformin, from the group of drugs called the biguanides. A newer group called the thiazolidinediones, or glitazones, includes rosiglitazone and pioglitazone. The balance of actions on different tissues is different between the glitazones and metformin, and they are sometimes used in combination. Metformin increases insulin sensitivity in the liver by inhibiting hepatic gluconeogenesis and thereby reducing hepatic glucose production.[8] Metformin may also increase peripheral insulin sensitivity by enhancing glucose uptake in the muscle. There have been concerns about the risk of lactic acidosis with metformin but the risk is probably much less than had been thought.[9] The thiazolidinediones decrease

insulin resistance in muscle and adipose tissue by activating the peroxisome proliferator-activated receptor g (PPAR-g) which increases production of proteins involved in glucose uptake. They also decrease hepatic glucose production by improving hepatic insulin sensitivity.

- drugs that delay the absorption of carbohydrates from the gastrointestinal tract, such as acarbose. Acarbose and its related drug, miglitol, are alpha-glucosidase inhibitors. These drugs reduce especially postprandial elevations in plasma glucose levels. They do not significantly lower fasting plasma glucose levels but cause a modest reduction in HbA1c.[10]

The Prescribing Support Unit (PSU), in collaboration with the York and Humber Public Health Observatory (YHPHO), produces data on use of diabetes drugs. The most used drug is metformin, with about 10 million prescriptions a year in England.[11] Its use has been rising steadily. Second come the sulphonylureas, with around 5 million prescriptions a year, with little change over the last five years. Third come the glitazones, with about 2.4 million prescriptions a year. They are newer drugs whose use has increased over recent years. In terms of cost per annum, the glitazones are by far the most costly, being recently-introduced drugs with no generic forms.

Insulin treatment comes in different forms;

- short-acting, with a rapid onset and short duration. There are two forms, the older soluble or “regular” short-acting insulins, and the newer short-acting analogues (lispro, aspart, glulisine). These are used for mealtime injections (often called “bolus” though the term is not universally popular).
- intermediate acting, such as isophane (or NPH).
- long-acting, again with two types, the older forms such as ultralente, and the newer long-acting analogues, glargine and detemir. These are usually given once a day in type 2 diabetes.

Mixtures of short-acting and intermediate acting are widely used. These can be mixed in the syringe by the patient prior to injection, but there are several pre-mixed preparations available which are more convenient. They are called biphasic.

The normal pancreas produces a little insulin throughout the 24 hours with additional peaks of insulin after food. In recent years, in an attempt to mimic this physiological pattern, more use has been made of the combination of a long-acting insulin to provide the basal insulin with injections of short-acting insulin at meal-times – usually referred to as a basal-bolus regimen.

In the UKPDS, insulin treatment started with a once daily injection of long-acting ultralente. If that was insufficient, short-acting insulin was added – in effect a form of basal-bolus.

The PSU/YHPHO prescribing data [11] show that the use of glargine increased very rapidly. In terms of number of prescriptions per annum, it overtook isophane insulin in the spring of 2004, and now runs at around 1 million a year, with isophane around 400,000 in the first quarter of 2007. Detemir was launched later than glargine, but has now probably overtaken isophane in numbers.

Table 1 shows the range of costs of diabetes drugs

Table 1 Costs for selected drugs

Drug	cost per annum (insulins assume 40 iu/day). Costs are rounded to nearest whole number
metformin 500mg x 4 a day	£39
gliclazide 80mg twice daily	£25

Drug	cost per annum (insulins assume 40 iu/day). Costs are rounded to nearest whole number
glibenclamide 5mg twice daily	£36
glimepiride 2m once daily	£69
soluble insulin 10 ml vial	£109
isophane insulin 10 ml vial (including mixtures)	£109
metformin modified release 4 x 500mg tablets/day	£166
biphasic insulins cartridges	£195 to £286
insulin aspart 10 ml vial	£286
glargine or detemir 10 ml vial or glargine pre-filled device	£379
metformin/pioglitazone 2 x850mg + 15 mg/day	£410
sitagliptin 100mg daily	£432
pioglitazone 45mg once daily	£480
rosiglitazone 4mg twice daily	£643
metformin/rosiglitazone combination	£682
exenatide 10mcg twice daily	£828

Source: Prescribing Support Unit/York and Humber PHO. [11]

Caveat: Prices of all drugs fluctuate and some of the above may be out of date.

1.2 The NICE guideline

The purpose of this assessment report is to support an update of the NICE guideline on type 2 diabetes, released in May 2008.[6] That guideline covers the full range of management of type 2 diabetes, whereas the update covers only the place of the new drugs. Some key recommendations and other aspects of the guidelines are listed below;

- targets for control. An HbA1c level of 6.5% or under was set for people with type 2 diabetes in general, but it was recommended that targets should be tailored to the needs of the individual, and might be higher than 6.5% (Recommendation 16)
- if HbA1c levels were above target, but pre-meal levels were well-controlled (<7.0 mmol/l), then consideration should be given to reduction of postprandial glucose levels (Recommendation 18)
- it was recommended that treatment start with lifestyle measures, but it was accepted that these would fail in many or most cases.
- first-line therapy (algorithm page 99) should be metformin for people who are overweight or obese. A sulphonylurea to be considered in those who were not overweight.
- if monotherapy failed a sulphonylurea should be added to metformin, or vice versa. In some people, a meglitinide analogue might be considered instead of a sulphonylurea. Glitazones should be considered only if hypoglycaemia was expected to be a problem (though if it was a problem during a trial of the sulphonylurea, there could be a switch to a glitazone)
- if on dual therapy and HbA1c remained above 7.5%, third line treatment with a glitazone or insulin should be added. However, at this point treatment with exenatide could be considered.
- once insulin was started, metformin and the sulphonylurea would be continued, but with re-consideration of the sulphonylurea if hypoglycaemia occurred.

- if control deteriorated, the insulin therapy would be intensified (and though not stated, it would be logical to withdraw the sulphonylurea).
- as regards the type of insulin, Recommendation 52 stated that the first choice should be human NPH insulin, taken at bedtime or twice daily according to need. Glargine should be considered in certain situations: those who required a carer to give the injections; those whose lifestyle is restricted by recurrent symptomatic hypoglycaemia; those who would otherwise need twice-daily basal injections. These situations are the same as those for glargine in Technology Appraisal 53.[12] (Detemir was excluded from the GDG considerations because it was expected to be the subject of a technology appraisal).
- as regards choice of glitazone, the GDG noted concerns over cardiovascular risks with rosiglitazone, but concluded that:

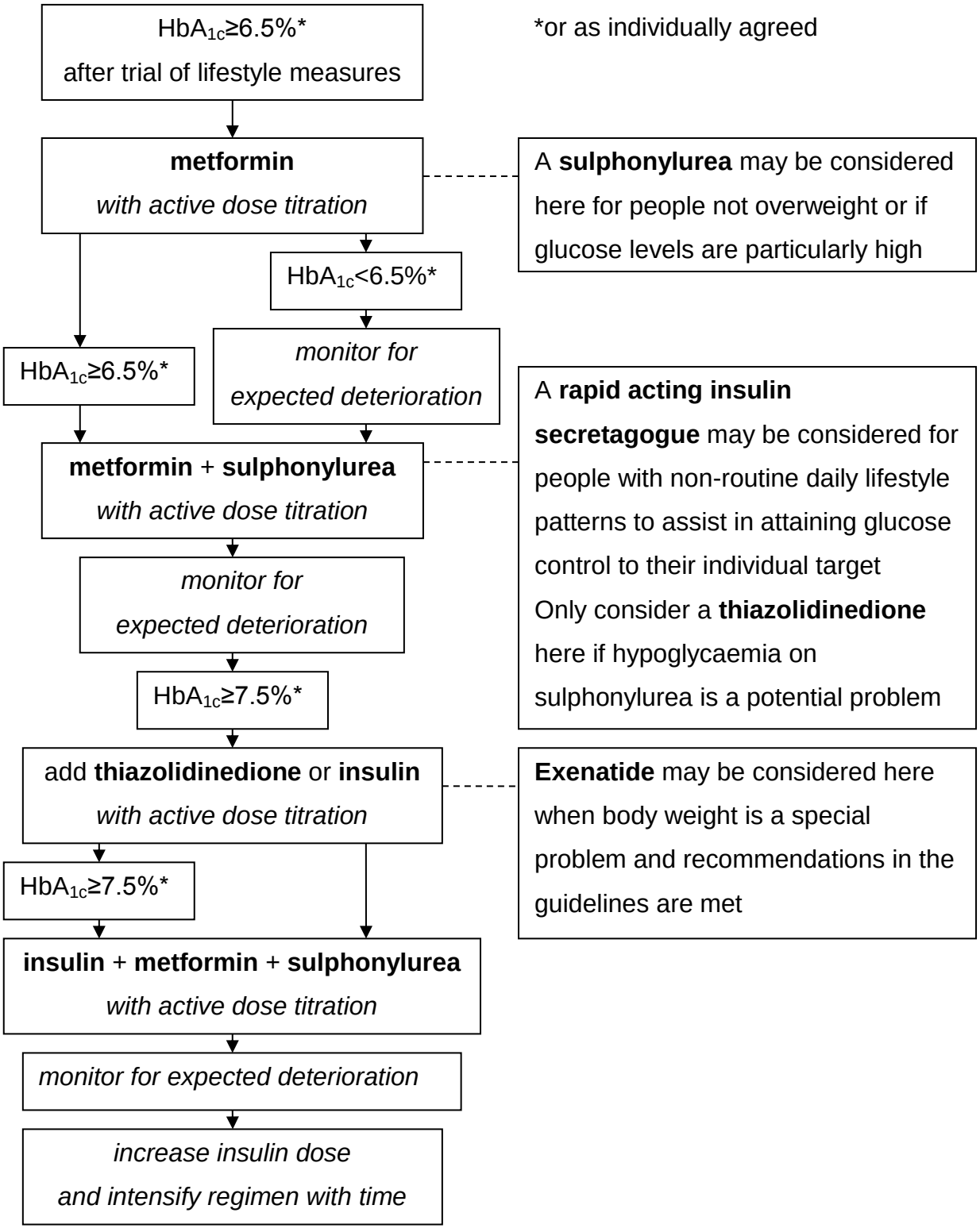
"On balance, despite reservations over rosiglitazone, it was felt not to be possible to unequivocally recommend a preference for pioglitazone in all circumstances, but rather to allow the choice of agent to rest with the person with diabetes and their advisor, taking ac account of the then current regulatory circumstances (which may yet change)."[6]

This is a little puzzling, since the risks appeared higher with rosiglitazone, and the economic analysis (page 127) concluded that "pioglitazone was estimated to yield a greater QALY gain at lower cost than rosiglitazone" and "rosiglitazone was consistently dominated by human insulin (both less effective and more expensive)".

- on exenatide, the guideline concluded that, on the evidence then available (page 135, section 10.4) "human insulin is a consistently more cost-effective option in any patient in whom it is an acceptable form of treatment." And recommendation R44 said that "Exenatide is not recommended for routine use in type diabetes". But R45 identified a situation in which exenatide might be considered, if all of the following applied: a BMI over 35; "specific problems of a psychological, biochemical or physical nature arising from high body weight"; inadequate blood glucose control (HbA1c >7.5%) with conventional oral agents after a trial of metformin and sulphonylurea; other high-cost medication (such as a thiazolidinedione or insulin injection therapy) would otherwise be started.

Figure 1 below shows the flowchart from the NICE guideline. Please note that this may not be the final version.

Figure 1: The Nice guideline algorithm



1.3 The use of insulin treatment

In the UK, there has been reluctance to switch to insulin in patients failing on oral agents. Two studies have used general practice databases to examine glycaemic control and treatment.

Calvert and colleagues[13] used data from the DIN-LINK database, from the years 1995 to 2005. DIN-LINK has anonymised date from 154 general practices. Calvert and colleagues obtained data on patients with type 2 diabetes, including the treatment they were on and their HbA1c levels. They were particularly interested in how long patients remained poorly controlled on oral agents before starting insulin. (The study was on behalf of Pfizer, to inform the NICE appraisal of inhaled insulin; Pfizer thought that one advantage of inhaled insulin would be to make it easier to persuade people to start insulin.)

Calvert and colleagues identified all patients with type 2 who were prescribed two or more types of oral agent, and looked at their HbA1c levels before and after the addition of another drug. Adding a second drug reduced HbA1c by about 1% (95% CI 0.95 to 1.05). Adding a third reduced it by a further 0.48% (0.37 to 0.59). Adding a fourth drug gave no further benefit. (We should note that this was before the arrival of the GLP analogues and the DPP-4 inhibitors).

When insulin was prescribed for the first time to those with poor control on oral agents, the initial drop in HbA1c was 1.3%, but 73% still had levels above the NICE target of 7.5% or less. The median time from addition of the last oral agent to the start of insulin therapy, for patients on two or more oral agents, was seven years. In those with poor glycaemic control following addition of the last oral drug, only 27% were prescribed insulin during the study. The implication is that many patients were left poorly controlled rather than being switched to insulin.

Rubino and colleagues (2007)[14] used another British GP database, The Health Improvement Network (THIN) database to identify patients with type 2 diabetes who were poorly controlled (at two levels, >8% and >9%) on oral agents, and who had not been treated with insulin. They then followed them to see how long it was before insulin was started.

Using the cut-off for poor control of HbA1c of 8% or over, they found 2501 eligible patients, mostly aged 50-79 years, and with duration of diabetes usually at least five years. Most had been on oral glucose lowering agents (OGLAs) for over five years. About 25% of these patients started insulin by two years, and 50% by 5 years. So transition was slow, and many were not transferred to insulin at all.

When OGLA failure was defined as HbA1c of 9% or over, they found 1691 patients who qualified. By 4.2 years, 50% had started insulin.

The presence of complications such as retinopathy had little effect on the time to insulin treatment. Those with retinopathy started insulin at a median of 4.6 years, those without at 5 years.

This study was also funded by Pfizer.

1.3.1 Why is there reluctance to use insulin?

In a previous technology assessment report for NICE, on inhaled insulins, we pondered upon why there should be reluctance.[15] There seemed to be reluctance amongst both patients and physicians. What follows is based on that TAR. Time did not permit a systematic review.

The DAWN (Diabetes Attitude Wishes and Need) study found that 55% of patients who have never had insulin treatment are anxious about it being required. The authors, Peyrot and colleagues (2005) [16] review previous studies of patient attitudes to insulin therapy. They note that these involve beliefs that;

"taking insulin:

- *Leads to poor outcomes including hypoglycaemia, weight gain and complications*
- *Means that the patient's diabetes is worse and that the patient has failed*
- *Means life will be more restricted and people will treat the patient differently*

- *Will not make diabetes easier to manage."*

It is important to note that insulin treatment is not just about injections, but a whole package of care including dietary adjustments, home blood glucose testing, and self-adjustment of insulin doses. It is likely that for most people, insulin injections are less troublesome than blood testing.

Changing to insulin does not mean that control will improve. Unpublished data from the Lothian audit show that the average HbA1c in type 2 diabetes mellitus patients on insulin is about 8.5%. (J McKnight, personal communication, presented at RCPE conference, September 2005). The average for those with type 2 diabetes mellitus on OGLAs is 7.5%.

Similarly, a study from seven European countries[17] found that only 9.5% of patients with T2DM who were on insulin had HbA1c <6.5%; another 44% had HbA1c levels of 6.5% to 7.5%; and 47% had levels over 7.6%.

One issue in insulin therapy is the provision of structured education programmes, such as DAFNE (Dose Adjustment For Normal Eating). Good education may reduce problems with insulin treatment.

1.3.2 What is the optimum treatment for people with Type 2 diabetes inadequately controlled on oral agents?

It seems clear from the literature that there are differences of opinion on management of people with type 2 diabetes who are not adequately controlled on oral agents. A working group drawn from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) produced a consensus statement in 2006.[18] Some extracts from this statement give an impression of the problems;

"the availability of the newer agents has provided an increased number of choices for practitioners and patients and heightened uncertainty regarding the most appropriate means of treating this widespread disease. Although numerous reviews on the management of type 2 diabetes have been published in recent years, practitioners are often left without a clear pathway of therapy to follow."

"The most appropriate target levels for blood glucose, on a day-to-day basis, and HbA1c, as an index of chronic glycaemia, have not been systematically studied."

They noted the different target levels proposed by the various bodies, and reached a consensus that,

"an HbA1c of over 7% should serve as a call to action to initiate or change therapy"

They recommended that insulin should be initiated with either bedtime intermediate-acting insulin, or once daily long-acting insulin; metformin should be continued.

Goudswaard and colleagues,[19] in a Cochrane review, concluded that combinations of insulin and oral hypoglycaemic agents should be the starting point for people with type 2 diabetes who required insulin. Their review preceded the studies on long-acting analogues such as glargine and detemir. The oral agents most commonly used in the trials they found were sulphonylureas; only 7% used metformin alone.

Douek and colleagues (2005)[20] from the Metformin Trial Group carried out an RCT of adding metformin or placebo in people with type 2 diabetes who had been switched to insulin because of poor control. Continuation of metformin resulted in less weight gain, lowered insulin requirement and improve glycaemic control.

Aviles-Santa and colleagues (1999)[21] also showed that adding metformin to an insulin regimen in people with type 2 diabetes reduced HbA1c by 0.9% compared to placebo. Insulin

requirement was 29% lower, and the weight gain of 3.2kg, seen in the placebo group, was much more than in the metformin group (0.5kg).

Strowig and Raskin[22] carried out a review of combination therapy with insulin and either metformin or a glitazone, or both. Details of methods are not given and it was probably not systematic. They also concluded that it was worthwhile continuing an insulin sensitiser in type 2 diabetes patients switched to insulin. Because metformin and glitazones have different balances of sites of preferential action (acting on glucose production and glucose disposal), they also made the case that triple therapy should also be considered. Bailey (2005) also supported combination therapy with metformin and a glitazone for reducing insulin resistance in type 2 diabetes.[23]

Gerstein and colleagues (2006)[24] randomised poorly controlled (HbA1c 7.5 to 11%) patients to continue oral agents or to switch to glargine, in the Canadian INSIGHT study. Those treated with glargine achieved lower HbA1c and non-HDL cholesterol, and greater satisfaction, but more weight gain. However only 17.5% of patients on glargine reached the target of two or more consecutive HA1c levels of 6.5% or under. One weakness of the study was that at baseline, about 17% of the patients had not been treated with any oral agent; another 40% were on oral monotherapy.

Hayward and colleagues (1997)[25] noted that results from trials of insulin therapy in type 2 diabetes showed it to be efficacious, but thought that these results might not be replicated in routine care. In a very large study (8668 patients with type 2 diabetes) they found that "insulin therapy was rarely effective in achieving tight glycemic control". Two years after starting insulin therapy, 60% still had HbA1c levels of 8% of greater; 25% had levels between 8.0 and 8.9%, 20% between 9.0 and 9.9%, and 15% had levels over 10%. These are similar to the population-based audit from Lothian.

The observation that starting insulin in routine care usually fails to give good control in people with type 2 diabetes failing on oral agents, is presumably one reason why the physicians in the DAWN study27 showed considerable resistance to starting insulin therapy in type 2 diabetes – only about half of the physicians thought that insulin would be useful.

Yki-Jarvinen and colleagues (2006)[26] came to similar conclusions in people with T2DM who were obese (defined in this study as BMI over 28.1 kg/m2) – insulin did not improve control. In many of these patients, poor control is associated with overweight or obesity.

Aas and colleagues (2005)[27] tried another approach, randomising patients with poorly controlled type 2 diabetes to insulin or to a lifestyle intervention (exercise and diet counselling). Lifestyle intervention was as effective in glycaemic control but also resulted in weight loss. In a follow-up study in 2006, the authors also noted that lowering HbA1c by lifestyle measures had more beneficial effects on adipokine levels than when insulin therapy achieved the same lowering, which may result in a lower cardiovascular risk.[28] However numbers in this study were small (38 in total), and it needs to be replicated with larger numbers.

1.3.3 Beta cell mass

As mentioned above, by the time of diagnosis of type 2 diabetes, beta cell function is considerably impaired. An important issue is whether any treatments can preserve the remaining beta cell function, or promote regeneration.

Conversely, it is important to know if any treatments might accelerate beta cell decline. In the ADOPT trial, patients were randomised to monotherapy with glibenclamide, metformin or rosiglitazone. Outcomes included failure of monotherapy. By 5 years, 34% of the glibenclamide group had failed, compared to 21% on metformin and 15% on rosiglitazone.[29] Aston-Mourney and colleagues [30] have argued, based on this trial and basic science studies, that it may be harmful to force the beta cell to produce more insulin, and that doing so may

cause earlier beta cell death. The implication might be that drugs which are insulin-sensitisers rather than insulin secretagogues, may help to preserve beta cell function or mass, by reducing the pressure to produce more insulin. However, in the UKPDS [4] the slopes of rises in blood glucose were similar for metformin and sulphonylureas, which does not support the sulphonylurea harm theory.

Meier [31] has recently reviewed the evidence on beta cell mass, and the hypothesis that "resting" the beta cell would help, but concludes that;

"as yet, there is no direct evidence for the induction of beta cell apoptosis (death) by sulfonylurea drugs or for the preservation of beta cell mass by either metformin, glitazones or exogenous insulin in patients with type 2 diabetes."

1.4 Decision issues

This technology assessment report is being produced to assist the NICE Short Guideline Development Group, whose task is to update the 2008 NICE Guidelines for the management of type 2 diabetes. The update is required because of a number of drug developments, namely;

- The glucagon-like peptide 1 (GLP-1) analogues
- The dipeptidyl peptidase 4 (DPP-4) inhibitors
- The long-acting insulin analogues, which are not new, but where the current NICE guidance needs reviewed
- Safety concerns over the glitazones.

The evidence on clinical effectiveness will be dealt with separately for each drug group, in chapters 2 to 6. The literature on economic studies of new drugs for diabetes will be reviewed in chapter 7, and the cost effectiveness modelling of the new drugs will be in chapter 8.

2 Chapter 2 The glucagon-like peptide-1 analogue; exenatide

The glucagon-like peptide-1 analogues are a new class of oral glucose lowering drugs that mimic the endogenous hormone, glucagon-like peptide (GLP-1). GLP-1 is an incretin, a gastrointestinal hormone that is released into the circulation in response to ingested nutrients from food. The mechanism by which food stimulates GLP-1 release from intestinal endocrine cells is not known; however, it may be under the control of neuroendocrine pathways. The effect was discovered after it was noted that the stimulation of release of insulin from the pancreas was greater after oral glucose than after an equivalent amount given intravenously.[32]

Endogenous GLP-1 has a number of actions.[33] It stimulates insulin secretion[34], but only in a glucose-dependent manner, so that insulin is not released if glucose is low. The incretin effect stops once the plasma glucose is down to 3 mmol/l.[32] It also suppresses glucagon secretion, delays gastric emptying [35] and reduces appetite. It also increases insulin biosynthesis[36,37]. Therefore, it controls plasma glucose level in a number of ways.[38] The reduction of glucagon secretion in type 2 diabetes is also glucose-dependent.[39,40]

Natural GLP-1 has been shown to affect plasma glucose levels when given by subcutaneous injection[41]. However it is rapidly broken down by the enzyme dipeptidyl peptidase IV (DPP-4), resulting in a half-life of 1 to 2 minutes.[40,32,33] So the endogenous form could only be used via a continuous infusion, and therefore would be impractical for treatment.

The GLP-1 analogues, of which only exenatide is currently available, have the same actions as GLP-1 but are resistant to breakdown by DPP-4. This gives them a much longer half-life than endogenous GLP-1. Other drugs are coming, with liraglutide expected to be licensed in 2009.

Exenatide has the following actions: [42,43]

- Increasing glucose-dependent insulin release
- Suppressing glucagon secretion in situations where that is inappropriate, such as when glucose level is high
- Slowing of gastric emptying (which will slow glucose absorption after meals)
- Reduction of appetite, and hence reduction of food intake
- Restoration of first phase insulin secretion in people with type 2 diabetes.

Given these actions, it was hoped that the GLP-1 analogues would not be associated with the weight gain seen with some other diabetes drugs. Early reports suggested that weight loss might occur.[44,45]

2.1 Exenatide

Exenatide was originally isolated from the venom of the Gila lizard (Amylin Pharmaceuticals). The peptide from the lizard had similarities with GLP-1, but had greater affinity with the receptor and was resistant to DPP-4.

Exenatide is produced synthetically. It has a short half-life of about 4 hours, and has to be given (by injection) twice daily at present. The drug has been developed for diabetes treatment under the trade name Byetta - (Amylin Pharmaceuticals[45] and Eli Lilly[46]). A longer-acting form, exenatide LAR has been developed and is currently undergoing trials.[47,45] It may only have to be given weekly.

The second GLP-1 analogue will be liraglutide, produced by Novo Nordisk.[48] It is based on human GLP-1 but with an amino acid substitution and an attached acyl chain, which fosters binding to serum albumin, thereby delaying renal excretion. It has a longer half-life of about 11-13 hours, and so can be given once daily. (N.B. Because the GLP-1 analogues are designed to act mainly at meal-times, though they have some effect beyond those, they are not required during the night). Again, being a digestible peptide, it has to be given by subcutaneous injection. Liraglutide has not yet received a license for use in the UK, and will not be further discussed in this report.

2.2 Criteria for considering studies for this review

Types of evidence

For efficacy, randomised controlled trials are the gold standard. Open label extension studies are useful to see if the effects persist, and for the development (or sometimes waning) of side-effects. The drop-out rate may also be a useful guide to tolerability.

For our purposes, we are interested mainly in trials which use standard UK practice as the comparator. Standard practice is set out in the current NICE guideline for type 2 diabetes National Insitute for Health and Clinical Excellence, 2008 2522 /id} and is shown in the flowchart in chapter 1.

Types of interventions.

Treatment for a minimum of 12 weeks with exenatide, exenatide long-acting or liraglutide. Twelve weeks is chosen because of the time it takes for glycaemic control to be reflected in HbA1c, but should be regarded as the minimum acceptable rather than satisfactory. Longer duration studies would be better.

The 2002 NICE guideline on management of type 2 diabetes (see flowchart) stated that for individuals with a BMI over 25 kg/m2, the first choice in addition to diet was metformin, and if that was insufficient, an insulin secretagogue should be added. In practice that would be a sulphonylurea; the other secretagogues, the meglitinide agonists, are little used in the UK.

So the most relevant comparisons are;

1. The addition of a GLP-1 analogue to standard combination therapy when that is insufficient to achieve good control, i.e.
    a. metformin + a sulphonylurea versus metformin + sulphonylurea + a GLP-1 analogue
    b. A variant might use two insulin sensitisers;
        i. metformin + glitazone versus metformin + glitazone + GLP-1
2. In those who cannot tolerate metformin, a glitazone might be used in combination therapy instead;
    a. sulphonylurea + a glitazone versus sulphonylurea + glitazone + GLP-1 analogue

One outcome of interest will be progression to insulin treatment.

3. Another option suggested in the NICE guideline was to add a glitazone to the metformin and sulphonylurea combination, i.e. triple therapy. If that fails, insulin treatment is the next step, usually with a long-acting basal insulin, with metformin and perhaps the other drugs continued. So another possible comparison would be to try a GLP-1 agonist instead of insulin;
    a. Metformin + sulphonylurea + glitazone + GLP-1 agonist versus basal insulin + metformin + sulphonylurea + glitazone.
4. In those who have started insulin recently, there could be a case for stopping insulin and trying a GLP-1 analogue, so a further comparison is;

   a. insulin (with or without oral agents) versus oral agents + a GLP-1 analogue
   b. This is not a licensed use. The FDA patient information sheet[49] states that;
   c. *"Byetta is not a substitute for insulin in patients whose diabetes requires insulin treatment".*
5. This comparison looks at adding exenatide to metformin monotherapy, and was included at the request of the GDG which felt that there were some overweight patients in whom the further weight gain likely with the usual second-line combinations of adding a sulphonylurea (or a glitazone) was so undesirable that a GLP1 agonist should be considered instead, given the likelihood of weight loss.
6. Ideally, the comparison would be of metformin + exenatide versus metformin + a gliptin but at the time of writing, no such trials had been done, so comparison 5 is:
   a. metformin + exenatide versus metformin alone.

2.3 Licensed indications

The licensed indications vary a little between Europe and the USA. The EMEA approved indications are;

"Byetta is indicated for the treatment of type 2 diabetes mellitus in combination with metformin, and/or sulphonylureas in patients who have not achieved adequate glycaemia control on maximmaly tolerated doses of these oral therapies".

The FDA approval includes the glitazones:[49];

"Byetta is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione, but have not achieved adequate glycemic control."

2.4 Current evidence for effectiveness of glucagon-like peptide analogues in type 2 diabetes

Appendix 2 shows all the trials. Most of the studies were parallel-group, randomised controlled trials (Barnett 2007[50] was a crossover trial). The majority of studies appear to have been conducted in North America and/or Europe, with the exception of one that was conducted entirely in Japan (Seino 2007[51]). Four studies (Barnett 2007[50], Davis 2007[52], Heine 2006[53] and Nauck 2007[54]) were reported as non-inferiority/equivalence trials.

2.4.1 Excluded studies

The studies in the Table 2 below were excluded for the reasons given. Some of these trials provided useful information, for example showing that the GLP-1 agonists were effective in lowering plasma glucose compared to placebo, or were early dose-ranging studies, but were not relevant to our key comparisons.

Table 2: Excluded GLP-1 trials

First author and year	Reason for exclusion
Exenatide trials	
Bunck 2007 [55]	Participants were on metformin monotherapy. In addition, it is not clear from the abstract whether they remained on metformin.
Buse 2004 [56]	Participants had failed on sulphonylurea monotherapy.
Trescoli-Serano 2005 [57]	Abstract only and few details. Doesn't say whether oral agents continued

First author and year	Reason for exclusion
Kim 2007 (exenatide LAR) [47]	No details yet and not licensed

2.4.2 Included studies

Seven trials were relevant for our purposes, and are listed below, under the relevant comparisons. The quality of the trials seems reasonable, though some details were not reported, and insulin when a comparator may not have been optimally used. Table 3 gives the details.

Table 3: Quality of included GLP-1 trials

Study	Method of Randomisation	Allocation Concealment	Blinding	Intention to Treat Data Analysis	Percentage who completed trial	Power Calculation	Similarity of Groups at Baseline	Sponsorship/Author Affiliation
Barnett 2007 (cross –over trial)	Computer generated central randomisation table	Yes	Open	Yes	Exenatide/Insulin glargine sequence: 80.9% Insulin glargine/exenatide sequence: 84.3%	Yes (non inferiority design)	yes	Authors from Eli Lilly and Amylin Pharmaceuticals. Funded by Eli Lilly.
Davis 2007 [52]	Not reported	Not reported	Open	No	Exenatide: 57.6% Insulin : 93.8%	Yes	Yes	Authors from Eli Lilly and Amylin Pharmaceuticals
DeFronzo 2005	Not reported	Not reported	Triple blind	Yes	Exenatide (10 ug): 82.3% Placebo: 78.8%	Yes	Yes	Funded by Amylin Pharmaceuticals, Eli Lilly Authors from manufacturer
Heine 2005 [53]	Central randomisation table	Yes	Open	Yes	Exenatide: 80.9% Glargine: 90.6%	Yes (non-inferiority design)	Yes	Funded by Amylin Pharmaceuticals, Eli Lilly Authors from manufacturer
Kendall 2005 [58]	Not reported	Not reported	Double blind	Yes	Exenatide (5ug): 84.1% Exenatide (10ug): 82.6% Placebo: 76.1%	Yes	Yes	Sponsorship from and author affilitation with Eli Lilly and Amylin Pharmaceuticals
Nauck 2007 [54]	Computer generated randomisation table	Yes	Open	Yes	Exenatide: 78.7% Biphasic Insulin aspart: 89.9%	Yes (non-inferiority design)	Yes	Some authors from Amylin Pharmaceuticals and Eli Lilly
Zinman 2007 [59]	Central randomisation table	Yes	Double blind	Yes	Exenatide: 71.1% Placebo: 85.7%	Yes	Yes	Sponsorship by Eli Lilly and Amylin Pharmaceuticals

Comparison 1- addition of GLP-1 analogue to dual combination therapy

Kendall 2005

Kendall and colleagues[58] recruited 733 people with type 2 diabetes whose control was inadequate (HbA1c 7.5 to 11%) on dual therapy with metformin and a sulphonylurea. Their average age was 55 years (range 22 to 77), and mean BMI was around 34 kg/m2. They were recruited from 91 centres in the USA, an average of 8 recruits per centre. Most were Caucasian, with about 11% Black and 16% Hispanic. Mean duration of diabetes was about nine years.

There were three arms – placebo controls, exenatide 5 μg BID and exenatide 10 μg BID (after four weeks on 5 μg).

Zinman 2007

Zinman and colleagues[59] recruited 233 patients whose control was inadequate on a glitazone with or without metformin, but about 80% were on metformin. They came from 49 centres in Canada, the US and Spain, an average of just under five per centre. Mean age was 56 (range 21 to 75), and their mean BMI was 34 kg/m2.

These patients came from a larger group of 435 who were screened for entry. Discontinuation rates differed, with 71% of the exenatide group completing compared to 86% of the placebo group. The commonest reason for discontinuation was adverse events (19 of 121 on exenatide versus 2 of 112 on placebo). Exenatide was started at 5 μg twice daily for 4 weeks, increased to 10 μg for the remaining 12 weeks.

Concerns about the study by Zinman and colleagues were raised by Malozowski 2007.[60] These included;

- the representativeness of the included patients. Their control was inadequate, but many were not on maximal doses of other oral drugs. Also, 21% were not on any metformin, which should be first-line therapy.
- The lack of reinforcement of lifestyle interventions such as diet; no details were given of educational input. (So care before starting exenatide does not appear to have been optimised).
- There was a significant drop-out rate especially in the exenatide group, with 71% completing the trial.
- Full details of adverse events were not published, nor details of whether there were any sub-groups more susceptible to the side-effects (though with their relatively small numbers, Zinman and colleagues would not have the power to do much in the way of subgroup analysis.)
- The study duration, 16 weeks, was too short in a chronic disease.

Comparison 2 – patients intolerant of metformin where a sulphonylurea plus glitazone combination was the standard arm comparator, versus that plus a GLP-1 analogue.

No studies were found.

Comparison 3 – insulin + oral agents versus GLP-1 analogue + oral agents

Heine 2005

Heine and colleagues[53] recruited 551 patients in 82 centres in 13 countries, an average of just under 7 per centre. Mean age was 59 (range 30 to 75) and mean duration of diabetes was 9.6 years. They were less overweight than in some other studies, with mean BMI 31

kg/m2. On dual therapy with metformin and sulphonylurea (at maximum doses), HbA1c was between 7 and 10%. Those with recent severe hypoglyaemia were excluded.

Patients were randomised to have glargine (starting at 10 units, titrated to achieve FBG <5.6 mmol/l) or exenatide (10 μg BID) added to their oral agents. The dosage of the oral drugs was fixed unless hypoglycaemia was a problem, in which case the sulphonylurea dose was halved. 19 % of the exenatide group and 10% of the glargine group withdrew from the study. The proportions withdrawing because of adverse events were 9.5% for exenatide and 0.7% for glargine.

Nauck 2007

Nauck and colleagues[54] compared twice daily exenatide with twice daily biphasic insulin (aspart 30/70) in 505 patients whose control was not good enough (mean HbA1c 8.6 %; inclusion range 7% to 11%) on dual therapy with optimal doses of metformin and sulphonylurea. Those with recent severe hypoglycaemia were excluded. The oral agents were continued in unchanged dosage, unless hypoglycaemia occurred, in which case the dose of sulphonylurea was halved in the exenatide group. (In the insulin group, the insulin was reduced).

As in other studies, those randomised to exenatide started on 5 μg twice daily and increased to 10 μg (if tolerated – it was in 80%) after four weeks. The dosage of biphasic aspart was left to each investigator to adjust, according to glucose control and hypoglycaemia.

The study was carried out in 13 countries but the number of centres is not given. The trial was powered for equivalence, defined as a difference in HbA1c of not more than 0.4%. Of the 505 randomised, 199 (79%) of 253 on exenatide and 223 (90%) of the 248 on insulin completed the study. The difference was mainly due to withdrawals because of side-effects – 20 withdrawals in the exenatide group and none in the insulin group.

Home[61] had concerns about the study by Nauck and colleagues, including:

- the exenatide regimen was optimised but the biphasic insulin was not. The total daily insulin dose was lower than usually seen (it was 24 units/day at the end of one year).
- blood glucose control was relatively poor in the insulin group, with a reduction of 0.9% in HbA1c, lower than seen in most recent treat-to- target studies of insulin in type 2 diabetes.
- puzzlement about the use of an aspart product, from a rival manufacturer to the sponsor of the study (Lilly), when they could have used their own similar product. Exenatide is made by Lilly, who also produce the Humalog biphasic insulin.

The authors[62] mounted a reasonable defence against most of these points, but could not explain why insulin doses were not raised in pursuit of better control.

Barnett 2007

Strictly speaking this study[50] does not meet our inclusion criteria, because it recruited patients with inadequate control on either metformin or a sulphonylurea, but we include it in order to have more than one trial against glargine, and hence more data on relative effect size. The study was carried out in 26 places in six countries (not including the UK) and recruited 138 patients, to a cross-over trial of 10 μg exenatide twice daily or glargine titrated to achieve a satisfactory fasting glucose level. The baseline HbA1c was 9%. Mean age was 55 years, and baseline BMI 31. It was funded by the manufacturer, Eli Lilly.

Comparison 4 – patients already on insulin: replacement by GLP-1

This comparison is included for completeness and interest, but note that it is not currently a licensed indication.

Davis 2007

Davis and colleagues[52] recruited 51 patients who were already on insulin (various forms, for about three years) in combination with oral agents (mostly metformin alone or with a sulphonylurea). Randomisation was 2:1 in favour of exenatide. Mean age was 53, mean BMI 34 kg/m2, and mean duration 10 years. The study was carried out in five centres in the USA (average 10 patients per centre).

There were more withdrawals in the exenatide group (14 of 33) than in those remaining on insulin (1 of 16). The commonest reason was loss of glycaemic control on exenatide.

An editorial by Rosenstock and Fonseca[63] made a number of criticisms, starting with the comment that "the scientific value is rather unclear, but the marketing appeal is obvious". This may be a little harsh, since one aim of the study was to see if people with type 2 diabetes who had relatively recently started insulin, could manage without it. More pertinent points were that insulin treatment was not optimised, and that the results were less successful than the paper implied;

"this study raises issues about commercial bias in study design, interpretation and reporting by the pharmaceutical sponsors."

Comparison 5 – addition of GLP-1 analogue to metformin monotherapy

DeFronzo and colleagues (2005) carried out a three-armed trial (the Exenatide 112 trial), in 336 patients, aged 19 to 78 years (mean 53 years), who had had diabetes for an average of about 6 years, in 82 sites in the United States. Baseline mean BMI was 34 and mean HbA1c 8.2%. The three arms were metformin plus one of placebo, exenatide 10 ug BID, and exenatide 5 ug BID. Only the standard dose of 10 ug BID is included here.

2.4.3 HbA1c results

These are shown in Table 4 below.

Table 4: HbAc1 results for GLP-1 trials

Study	Study Arm and Number randomised	HbA1c (%) baseline	Change from baseline (%)	P value from baseline	Difference between groups at end (Exenatide-Comparator 95% CI)	P value between groups	% Patients achieving HbA1c of ≤ 7%
Barnett 2007 (cross –over trial)	Exenatide/ Insulin glargine treatment sequence + MET or SU (n=68)	8.89 (SE 0.13)	-1.36 (SE 0.09)	P<0.001		NS	37.5% (Exenatide treated pts)
	Insulin glargine/Exenatide treatment sequence + MET or SU (n=70)	9.00 (SE 0.13)	-1.36 (SE 0.09)	P<0.001			39.8% (glargine treated pts)
Davis 2007	Exenatide + oral medications (n= 33)	8.0 (SD 1.2)	+0.3 (SE 1.5)	NS	0.4%	NS	
	Current Insulin regimen + oral medications (n=16)	8.3 (SD (0.9)	-0.1 (SE 0.7)	NS			
DeFronzo 2005	Exenatide (10 µg) + MET (n=113)	8.18 (SD 1.0)	-0.78 (SE 0.1)			P<0.002	46%
	Placebo + MET (n=113)	8.2 (SD 1.0)	+0.08 (SE 0.1)				13%
Heine 2005	Exenatide + MET + SU(n= 282)	8.18	-1.11		0.017 (-0.123 to 0.157)	NS	46%
	Insulin glargine + MET + SU (n=267)	8.23	-1.11				48%
Kendall 2005	Exenatide + MET + SU 5 ug (n=245)	8.5 (SD 1.0)	-0.55 (SE 0.07)			P<0.0001	24% [1]
	Exenatide + MET + SU 10 ug (n=241)	8.5 (SD 1.1)	-0.77 (SE 0.08)				30% [1]
	Placebo + MET + SU (n=247)	8.5 (SD 1.0)	+0.23 (SE 0.07)				7% [1]
Nauck 2007	Exenatide + MET + SU (n=253)	8.6 (SD 1.0)	-1.04 (SE 0.07)	P<0.001	-0.15 (-0.32 to 0.01)	NS (P=0.067)	32% [2]
	Biphasic insulin aspart + MET + SU (n=248)	8.6 (SD 1.1)	-0.89 (SE 0.06)	P<0.001			24% [2]
Zinman 2007	Exenatide + MET + TZD (n=121)	7.89 (SE 0.9)	-0.89		-0.98 (-1.21 to -0.74)	P<0.001)	62% [3] 30% [4]
	Placebo + MET + TZD (n=112)	7.91 (SE 0.8)	+0.09				30% [3] 8% [4]

1 For ITT patients with HbA1c level >7% at baseline
2 Accounting for HbA1c stratification at screening
3 For the per protocol sample, with HbA1c level >7% at baseline
4 For the per protocol sample who achieved a target HbA1c level ≤ 6.5% (with HbA1c level >7% at baseline)

The trials show that in those whose control is not good enough on dual therapy, addition of exenatide improved HbA1c by about 1% (Kendall 2005[58] and Zinman 2007[59]).

In the Kendall (2005)[58] trial, the changes in HbA1c at 30 weeks were greater in those whose baseline level was higher.

	Exenatide 5ug	Exenatide 10ug	Placebo	Significance
Baseline A1c <9% (read from graph Fig 2C)	-0.40	-0.55	0.35	Compared with placebo P<0.0001)
Baseline A1c ≥9 (read from graph Fig 2C)	-0.95	-1.40	0	Compared with placebo (P=< 0.0002)

When exenatide is compared with various insulin regimens, the results are similar, suggesting non-inferiority, though the issue of non-optimisation of the insulin treatment remains an issue.

2.4.4 Hypoglycaemia

Table 5 shows the frequency of hypoglycaemia.

Table 5: Frequency of hypoglycaemic events in GLP-1 trials

Study	Study Arm and Number	Incidence of hypoglycaemia % (n)	Overall hypoglycaemia rates (events/patient year)	Serious hypos	Noctural Hypo events	Daytime Hypos	Severe Hypoglycaemic episodes
Barnett 2007 (cross –over trial)	Exenatide + MET or SU	14.7%	1.9 [95% CI, 1.5-2.4]		0.4 event/ patient-year [95% CI, 0.2-0.7]		0 episodes
	Insulin glargine + MET or SU	25.2%	2.6 [95% CI, 2.2-3.2]		1.3 events/patient year [95% CI, 1.0-1.7]		8 episodes
Davis 2007	Exenatide + oral medications (n= 33)	39% (13)	1.72	0		11/13	1 patient treated with exenatide + SU had 3 severe hypos
	Current insulin regimen + oral medications (n=16)	38% (6)	0.97	0		4/6	
DeFronzo 2005	Exenatide (10 µg) + MET (n=113)	5.3%					0
	Placebo + MET (n=113)	5.3%					0
Heine 2005	Exenatide + MET + SU(n= 282)		7.3 [1]		0.9 event patient year [2]	6.6 event patient year [3]	4 pts
	Insulin glargine + MET + SU (n=267)		6.3		2.4 event patient year	3.9 event patient year	4 pts
Kendall 2005	Exenatide + MET + SU 5 ug (n=245)	19.2% (47)		1 case			
	Exenatide + MET + SU 10 ug (n=241)	27.8% (67)					
	Placebo + MET + SU (n=247)	12.6% (31)					
Nauck 2007	Exenatide + MET + SU (n=253)		4.7 (SE 0.7)		17% (44) [4]		
	Biphasic insulin		5.6 (SE 0.7)		25% (62)		

Study	Study Arm and Number	Incidence of hypoglycaemia % (n)	Overall hypoglycaemia rates (events/patient year)	Serious hypos	Noctural Hypo events	Daytime Hypos	Severe Hypoglycaemic episodes
	aspart + MET + SU (n=248)						
Zinman 2007	Exenatide + MET + TZD (n=121)	10.7% (13) [5]					0
	Placebo + MET + TZD (n=112)	7.1% (8)					0

1 Difference (Exenatide – glargine arms) = 1.1 (CI, -1.3 to 3.4) NS
2 Difference (Exenatide – glargine arms) = -1.6 (CI, -2.3 to -0.9)
3 Difference (Exenatide – glargine arms) = 2.7 (CI, 0.4 to 4.9)
4 p<0.038
5 Difference between groups, 3.6% [CI, -4.6 to 11.8%]

Definitions of hypoglycaemia used in the included trials.

- Barnett 2007 defined it as any sign or symptom due to hypoglycaemia, or a serum glucose concentration under 3.3 mmol/l. So asymptomatic hypos were included.
- Davis 2007 included any episode in which a patient felt they were experiencing a sign or symptom of hypoglycaemia, or a blood glucose under 3.4 mmol/l, irrespective of whether any symptoms were associated.
- De Fronzo 2005 based recording on symptoms which were confirmed by a plasma glucose under 3.3 mmol/l.
- Heine 2005 included both symptomatic episodes and biochemical ones.
- Kendall 2005 used symptoms that “may have been documented by a plasma glucose under 3.33 mmol/l”.
- Nauck 2007 included both symptomatic episodes and instances of blood glucose under 3.4 mmol/l during self-monitoring, whether or not the monitored episode was associated with any symptoms.
- Zinman 2007 also defined hypoglycaemia as either symptoms or self-monitoring readings.

As expected, the frequency of hypoglycaemia varied amongst studies. Severe hypoglycaemia was uncommon. There were no severe hypos in the Nauck 2007 and Zinman 2007 trials, and only one in the Kendall 2005 study.

In Barnett 2007, three patients experienced 8 episodes of severe hypoglycemia during insulin glargine treatment, whereas there were no episodes of severe hypoglycaemia during exenatide treatment.

Also exenatide-treated patients had significantly lower mean rates of overall hypoglycemia ($P = 0.039$) and nocturnal hypoglycemia ($P < 0.001$) compared with insulin glargine-treated patients. There were also no significant differences in rates of daytime hypoglycemia between exenatide and insulin glargine treatment

In the Davis 2007 trial, most hypoglycaemia occurred during daytime. Of the 13 exenatide patients who reported hypoglycaemia, 10 were also taking a sulphonylurea. Overall hypoglycaemia rates were higher in those with good control (exenatide 2.5 events per patient year; insulin 1.2 events per patient year).

In the Heine 2005 trial, the overall frequencies of hypoglycaemia were similar, but nocturnal hypoglycaemia was less frequent in those on exenatide. In those who achieved good control (HbA1c of 7% or less at week 26), 61% of the exenatide group and 68% of the glargine group reported at least one symptomatic hypoglycaemic episode, and 21% of those on exenatide and 43% of those on glargine reported at least one episode of nocturnal hypoglycaemia.

Although the nocturnal hypoglycaemia rate in the Nauck 2007 study was significantly lower in the exenatide group (see table), this was no longer statistically significant once adjusted for baseline HbA1c. Once the sulphonylurea doses were reduced, hypoglycaemia rates fell from 27 to 6 events per patient year.

2.4.5 Weight

Most studies reported weight loss with exenatide treatment. Results are shown in Table 6

Table 6: Weight changes in GLP-1 trials

Study	Study Arm and Number randomised	Weight in kg (SD) at baseline	Change in kg (SE) from baseline	P value from baseline	Difference in kg between groups at end (Exenatide-Comparator 95% CI)	P value between groups
Barnett 2007 (cross –over trial)	Exenatide/ Insulin glargine treatment sequence + MET or SU (n=68)	85.6 (SE 2.0)	Exenatide treated -1.6 [SE 0.3]		-2.2 [SE 0.3] 95% CI, -2.8 to -1.7;	P<0.001
	Insulin/glargine/Exenatide treatment sequence + MET or SU (n=70)	84.0 (SE 2.0)	Glargine treated +0.6 [SE 0.3]			
Davis 2007	Exenatide + oral medications (n= 33)	95 (17)	-4.2 (3)	p<0.001		P < 0.001
	Current insulin regimen + oral medications (n=16)	102 (19)	+0.5 (1.7)	p = NS		
DeFronzo 2005	Exenatide (10 µg) + MET (n=113)	101 (SE 2)	-2.8 (SE 0.5)			P ≤ 0.001
	Placebo + MET (n=113)	100 (SE 2)	-0.3 (SE 0.3)			
Heine 2005	Exenatide + MET + SU(n= 282)	87.5 (16.9)	-2.3		-4.1 (-4.6 to -3.5)	P < 0.0001
	Insulin glargine + MET + SU (n=267)	88.3 (17.9)	+1.8			
Kendall 2005	Exenatide + MET + SU 5 ug (n=245)	97 (19)	-1.6 (0.2)			P ≤ 0.01 vs placebo
	Exenatide + MET + SU 10 ug (n=241)	98 (21)	-1.6 (0.2)			
	Placebo + MET + SU (n=247)	99 (19)	-0.9 (0.2)			
Nauck 2007	Exenatide + MET + SU (n=253)	85.5 (15.7)	-2.5 (0.2)	P <0.01	-5.4 (-5.9 to -5.0)	P <0.001
	Biphasic insulin aspart + MET + SU (n=248)	83.4 (15.6)	2.9 (0.2)	P <0.01		
Zinman 2007	Exenatide + MET + TZD (n=121)	97.5 (18.8)	-1.75		-1.51 (-2.15 to -0.88)	P <0.001
	Placebo + MET + TZD (n=112)	96.9 (19)	-0.24			

2.4.6 Does nausea cause the weight loss?

Maggs and colleagues (2005)[64] carried out an analysis of patients in three trials (Buse 2004[56], De Fronzo 2005[65] and Kendall 2005[58]) to see if the weight loss with exenatide was related to the nausea. Severe nausea was found in only 4%. They found little correlation between nausea and weight loss (or HbA1c). In the extension studies (to 52 weeks), the majority of patients had very little nausea, but lost the same amount of weight as the more nauseated subgroups.

Heine and colleagues[53] found that although the magnitude of weight reduction tended to be greater in patients taking exenatide who experienced longer durations of nausea, patients who did not report any episodes of nausea during the trial (n = 120) still demonstrated a mean weight change of -1.9 kg (CI, -2.5 to -1.4 kg)

2.4.7 Adverse events other than hypoglycaemia

Table 7 shows the most frequent side-effects.

Table 7: Most frequent side-effects in GLP-1 trials

Study	Study Arm and Number randomised	Nausea	Vomiting	Diarrhoea	Any Adverse Event	Discontinuation due to adverse events
Barnett 2007 (cross –over trial)	Exenatide treatment	42.6%	9.6%		65.4%	11
	Insulin glargine treatment	3.1%	3.1%		52.8%	1
Davis 2007	Exenatide + oral medications (n= 33)	48.5%			79%	5 pts
	Current insulin regimen + oral medications (n=16)	12.5%			56%	0 pts
DeFronzo 2005	Exenatide (10 µg) + MET (n=113)	45%	12%	16%	2.7% (serious) 9.7% (severe)	7.1%
	Placebo + MET (n=113)	23%	4%	8%	3.5% (serious) 8.8% (severe)	0.9%
Heine 2005	Exenatide + MET + SU (n= 282)	161 (57.1%) *	49 (17.4%) *	24 (8.5%)**		9.5%
	Insulin glargine + MET + SU (n=267)	23 (8.6%)	10 (3.7%)	8 (3.0%)		0.7%
Kendall 2005	Exenatide + MET + SU 5 ug (n=245)	96 (39.2%)	36 (14.7%)	25 (10.2)		14 (5.7%)
	Exenatide + MET + SU 10 ug (n=241)	117 (48.5%)	33 (13.7%)	42 (17.4)		22 (9.1%)
	Placebo + MET + SU (n=247)	51 (20.6%)	11 (4.5%)	16 (6.5%)		11 (4.5%)
Nauck 2007	Exenatide + MET + SU (n=253)	84 (33.2%)	38 (15.0%)	24 (9.5%)	179 (70.8%)	Together, 5.1% of patients withdrew because of gastrointestinal-related adverse events
	Biphasic insulin aspart + MET + SU (n=248)	1 (0.4%)	8 (3.2%)	5 (2.0%)	123 (49.6%)	
Zinman 2007	Exenatide + MET + TZD (n=121)	48 (39.7%) [1]	16 (13.2%) [2]	7 (5.8%) [3]	92 (76.0%) pts reporting ≥ 1 AE)	19 (16%)

Study	Study Arm and Number randomised	Nausea	Vomiting	Diarrhoea	Any Adverse Event	Discontinuation due to adverse events
	Placebo + MET + TZD (n=112)	17 (15.2%)	1 (0.9%)	3 (2.7%)	73 (65.2%) pts reporting ≥ 1 AE)	2 (2%)

** p <0.001 compared to insulin glargine arm ** p 0.006 compared to insulin glargine arm*
1 The between-group difference in % of patients (exenatide minus placebo) was 24.5 % (CI, 12.7 to 36.3%)
2 The between-group difference in % of patients (exenatide minus placebo) was 12.3 % (CI, 5.2 to 19.5 %).
3 The between-group difference in % of patients (exenatide minus placebo) was 3.1 % (CI, -2.9 to 9.1 %).

The most striking finding is the high frequency of nausea with exenatide, with vomiting not uncommon. However the number who had to stop exenatide because of side-effects was much lower. Most nausea was mild, and the frequency decreased over time. For example, Heine and colleagues reported that 55% of patients reported nausea in the first eight weeks, but only 13% did so in the last 8 weeks. However 18 patients from the exenatide group withdrew because of nausea (compared to one in the insulin group). Heine and colleagues reported the frequency of mild, moderate and severe nausea to be 33%, 20% and 5% respectively.

Kendall and colleagues also reported that the frequency of nausea diminished over time, and only 4% had to withdraw because of it.

Zinman and colleagues reported that 9% of the exenatide group withdrew because of nausea, but that most nausea was mild (44%) or moderate (41%) and that it declined over time.

2.4.8 Cardiovascular risk factors.

Three trials reported lipid and blood pressure data.

DeFronzo 2005 reported that exenatide treatment was not associated with an increased incidence of cardiovascular, hepatic, or renal adverse events. Also no changes in plasma lipids, laboratory safety parameters, heart rate, blood pressure, or electrocardiogram variables were observed between treatment arms.

Nauck and colleagues reported that HDL was higher, by 0.04mmol/l, with insulins, but that blood pressure fell with exenatide (systolic by 5 mm/Hg and diastolic by 2mm) but did not change with insulin.

Zinman and colleagues found no significant differences in lipids and blood pressure.

2.4.9 Other outcomes.

Patient reported outcomes from the Barnett 2007 trial were reported by Secnik and colleagues in a poster presented at IDF in 2006.[66] Responses to the health outcome intruments the Psychological General Well-Being Index (PGWB), Diabetes Symptom Checklist-Revised (DSC-R), EuroQol instrument score (EQ-5D), Treatment Flexibility Scale (TFS), and Hypoglycaemia Fear Survey (HFS) were examined. No statistically significant between-group differences between twice daily exenatide and glargine were found on any of these measured health outcomes.

Secnik Boye and colleagues (2006)[67] reported some patient reported outcomes from the Heine trial, including EQ5D, the vitality scale of the SF-36, the Diabetes Symptom checklist, and the Diabetes Treatment Satisfaction Questionnaire. No differences were found, suggesting that the greater number of injections with exenatide (twice daily versus once for glargine), and the frequent (at least initially) nausea was not enough to affect overall satisfaction, perhaps because those were balanced by weight loss on exenatide (on average, 2.3 kg) versus gain on insulin (mean 1.8kg).

An abstract from the Nauck 206 trial by Yurgin and colleagues (2006)[68] also reported EQ5D and SF36 data, stating that the exenatide group showed some improvement whereas the biphasic aspart group showed no change.

Lower dose exenatide

The standard dose of exenatide is 10 μg BID, but there are some results on 5μg BID from two of the trials.

Table 8: Comparison of low dose and standard dose results

	5 μg BID	10 μg BID	Placebo
De Fronzo			
HbA1c change	- 0.4%	- 0.8%	
% reaching < 7%	32%	46%	13%
weight	- 1.6kg	-2.8 kg	-0.3kg
Kendall			
HbA1c change	- 0.55%	- 0.77%	+ 0.23%
% <7%	24%	30%	7%

Hence those who can tolerate the starting dose but not the full one, still get some benefit. (NB the cost appears to be the same, so the benefit/cost ratio is higher).

2.4.10 Follow-up studies - open label extensions

Klonoff and colleagues (2008)[42] report results in people who had been on exenatide for at least three years. The participants were from the three 30-week studies (Buse 2004[56], De Fronzo 2005 [65] and Kendall 2005 [58]) only one of which met our inclusion criteria for this review. However the pooled open label follow-up can provide useful data on duration of efficacy, and side-effects.

The withdrawal rate was high. Of 527 eligible patients, 310 withdrew. The reasons for withdrawal included adverse events (11%), poor control (3%), and patient or investigator decision (41% - reasons not given).

Weight loss was maintained amongst the 41% (217) who stayed in the follow-up study. The mean weight loss at 3 years was 5.3kg. 84% of patients lost weight. Reductions in HbA1c were also sustained (but this may be because those in whom it rose again left the study). Total cholesterol fell by 5% and triglycerides by 12%, presumably because of the weight loss, because there was a correlation between weight loss and cardiovascular risk factors.

The most frequent adverse effect (in 59%) was nausea, usually mild. Next came hypoglycaemia, but only in those treated with a sulphonylurea. Upper respiratory infections were common (36%) but the significance of that cannot be assessed without a control group. There were no serious side-effects other than a few severe hypoglycaemic episodes. So exenatide appears safe, but the high drop-out rate reduces the value of the study.

2.4.11 Results from routine care.

Rather different results were found in routine care by Wolfe and King (2007).[69] Two hundred consecutive exenatide-treated patients included 56 treated for 12 months. The nadir of weight occurred at 6 months. Few details are given of later weight loss in this ADA conference abstract, but the suggestion is that there was a plateau after six months.

Loh and Clement (ADA poster 2007)[70] reported a small follow-up study of 30 patients with type 2 diabetes treated with exenatide, some in addition of oral antidiabetic drugs (OADs), others in addition to insulin. At one year, there was weight loss (mean 2 kg; p=0.0033) but no significant reduction in HbA1c overall. Maximum weight loss occurred by 7 months, with most patients regaining weight over months 7 to 12. Half the patients had stopped exenatide by 12 months, because of therapeutic failure or side-effects. Loh and Clement conclude that in the “real world”, exenatide may not give as good results as seen in trials.

Yoon and colleagues in a conference abstract (ADA 2008), reported use of exenatide added to insulin. In a case series of 226 patients who started exenatide, 34 (15%) stopped within 3 months due to adverse effects.[71] Another 78 discontinued it later, mainly due to side effects or lack of efficacy. The final analysis of those who had used it for more than a year (116)

showed weight loss of 6 kg, and a 20% reduction in insulin dosage. Eleven patients with an initial mean insulin dose of 17 units per day were able to stop insulin.

Another study from routine care, reported by Bhushan and colleagues at the ADA 2008 conference,[72] followed 201 patients for 16 weeks; all received exenatide in addition to previous treatment (details of which not given). Weight loss was seen in 69%, and averaged about 2 kg. Total cholesterol fell by 6 mg/dl. Blood pressure was unchanged.

It seems logical that exenatide be combined with insulin, although this is not a currently licensed indication. In an abstract from the recent European Association for the Study of Diabetes conference, Govindan and colleagues[73] presented a small case series from Wolverhampton, of 27 obese patients (mean BMI 43 at baseline) who were already on insulin but poorly controlled (mean HbA1c 8.8%). About half had nausea on exenatide, but only three had to stop it. The mean weight fell from 128 kg to 115 kg after three months; BMI from 43 to 40; and insulin dose from a mean of 170 units/day to 36 units/day. The average insulin dose reduction comes about because ten patients could stop it altogether, although mean HbA1c did not improve much (by only 0.3%; NS). Longer follow-up might show greater benefit, and it suggests that trials of combined exenatide and insulin therapy are justified.

Also from the EASD conference, Wintle and colleagues (from Amylin and Lilly)[74] presented data from diabetic care records from the General Electric database, on 2086 patients treated with exenatide for six months or more. Patients had previously been on metformin, sulphonylurea or glitazone monotherapy (about 30%), or on dual therapy (38%) or triple therapy (34%), but were not well controlled (mean HbA1c 8.4% and BMI 38.5).

Exenatide reduced HbA1c by 0.9% in those who had been on monotherapy, but by less (0.5 to 0.8%) in those who had been on combination treatment.

Kendall and colleages (Amylin and Lilly)[75] reported a pooled analysis of two years of exenatide treatment. Patients were split into three groups according to pattern of weight loss – one group which lost none (they gained about 1 kg – but since their HbA1c fell by over 1%, they were presumably taking the exenatide, suggesting that compliance was not the issue); a second group (34%) which lost weight quite quickly (about 4 kg by week 12); and a third group (46%) which lost as much weight as the second group, but who did so more slowly. Groups 2 and 3 lost on average 6 kg by two years.

In the group which did not lose weight, HbA1c fell by about 1.2% but started rising again in the second year, to a drop of about 0.7% (from graph). In groups 2 and 3, the fall in HbA1c of about 1.5% was more sustained – about 1.5% reduction at 52 weeks and 1.3% at 104 weeks.

This finding might have implications if NICE recommended a stopping rule for exenatide, since it could be stopped in those in whom it was least effective (no weight loss), thereby improving the cost-effectiveness.

2.4.12 Exenatide LAR

The exenatide LAR formulation has been studied in a 15 week phase II trial (Kim 2007) in patients with type 2 diabetes.[47] The trial reported that a 2 mg dose of exenatide LAR showed a reduction in HbA1c of 1.4% (relative to placebo) which the authors say is approximately twice as great as that seen with twice daily injections of conventional exenatide. Preliminary results have suggested that the LAR formulation is also better tolerated than the original formulation, with less nausea, and (in the 2mg form) is associated with greater weight loss; however patient numbers were small. Results from other trials are awaited. The Amylin websit [45] reports an unpublished 30-week RCT of long-acting exenatide versus twice daily Byetta, and states that “results showed that exenatide once weekly demonstrated powerful glucose efficacy, complemented by striking weight loss.”

This trial is presumably the DURATION trial, recently described in two abstracts. ADA abstract Drucker and colleagues reported the 30 week results in brief.[76] They showed that once weekly exenatide reduced HbA1c slightly more than twice daily; 1.9% versus 1.5%. Seventy seven percent of the once weekly group achieved HbA1c less than 7.0%, compared to 61% for the twice daily. The trial recruited 295 patients who were poorly controlled (mean HbA1c 8.3%), but most were on no oral drugs (15%) or monotherapy (45%). Only the 40% on two oral agents are relevant to this review.

However, the trial clearly suggests that the future lies with once weekly exenatide. No details on cost are yet available, but some economies would be expected compared to twice daily injections.

The second abstract is from EASD[77] and is a 22-week open label follow-up of 241 of the DURATION patients by Buse and colleagues (the same team as Drucker and colleagues). Much of the abstract is about the patients who switched from twice daily to weekly, but the 52 week HbA1c results in the original once weekly group are reported in brief as being sustained – reduction at 52 weeks of 2% (1.9% at 30 weeks).

2.4.13 GLP-1 agonists and beta-cell function

Rodent studies have reported that liraglutide can increase beta-cell mass.

Gallwitz (2006)[78] has reviewed some of the animal and in vitro studies. The animal studies are mainly in rats, with a couple in mice. The evidence suggests that beta-cell growth is stimulated and that apoptosis is reduced. In isolated human islets, GLP-1 expands beta-cell mass. However he found no evidence regarding beta-cell mass in humans.

Xu and colleagues[79] reported that in rats made diabetic by partial pancreatectomy, exenatide treatment improved diabetic control, and that this was related to an increase in beta-cell mass (assessed histologically). Interestingly, the improved control was seen even after exenatide was stopped after 10 days. Gedulin and colleagues[80] also reported an increase in beta-cell mass in rats after exenatide treatment.

Tourrel and colleagues[81] treated newborn rats made diabetic with streptoxozotocin with exenatide and again noted an increase in betal cell mass, which persisted (though the beta-cells were less responsive to glucose).

If these findings are confirmed in humans, that would be of great importance, because it would suggest that the progressive nature of type 2 diabetes[4,5] could be halted. Barnett (2007) [38] and Holst (2008) [82] both note that if the GLP-1 analogues could increase beta-cell mass, there would be an argument for treatment early in the disease, before too many beta-cells had been lost.

However there are few data on the effect in humans – some very short experiments on islet cells in vitro, reviewed by Wajchenberg[83], who concludes that there is as yet no clinical evidence that the GLP-1 analogues protect beta-cells.

Bunck and colleagues,[84] in an ADA abstract from their RCT of exenatide versus glargine[85] reported that the beneficial effects seen on exenatide were not sustained – 5 weeks after stopping exenatide all the improvements had gone, which may suggest that beta-cell function was not improved.

Further research is required, ideally with some means of determining at an early stage (2-3 years?) whether beta-cell mass is maintained in humans with type 2 diabetes.

2.5 Discussion

Barnett (2007) [38]comments that:

"The appeal of exenatide therapy is that it provides glycaemic control with concomitant weight loss (as opposed to rapid or short-acting insulins which tend to cause weight gain), and, when not used with a drug that increases circulating insulin levels, does not cause hypoglycaemia."

The evidence to date shows that the GLP-1 analogues can provide a useful improvement in glucose control when added to dual treatment with oral drugs, and that at least in the short term, they can be an alternative to starting insulin. How long this effect would last, is not known. If we assume that the disease will steadily progress, as shown in UKPDS 16[4], then some of the benefit will be lost since the beta-cells will no longer be there to be release insulin. Other benefits such as delayed gastric emptying may continue, which may help control post-prandial hyperglycaemia.

The glucose-dependent nature of the insulin release means that hypoglycaemia should be less of a problem, but the differences in the trials were not marked.

Weight loss is a useful feature in the trials, though perhaps seen less in routine care.

The drawbacks are the need for injections (twice daily with exenatide and once a day with liraglutide), the high rate of side-effects (especially nausea), and the cost.

Injecting a foreign peptide could lead to antibody formation, but Barnett (2007)[38] notes that such antibodies were common by 30 weeks but did not appear to reduce efficacy.

A review by the well-respected Prescrire International group from France concluded that exenatide was an alternative to starting insulin in poorly controlled type 2 diabetes patients, but that there was no evidence as yet that it was better, and that given the much greater experience with insulin, that should be preferred.[86]

The German Institute for Quality and Efficiency in Health Care (Institut fur Qualitat und Wirtschaftlickeit im Gesundheitswesen or IQWiG) issued a report on exenatide in 2007.[87] Their review of exenatide addressed two questions;

- is it worthwhile to add exenatide to therapy with metformin and/or a sulphonylurea?
- how does adding exenatide compare with other additional treatments?

The review identified five trials. These included the Kendall 2005, Nauck 2007, De Fronzo 2005 and Heine 2005 studies included in our TAR. The other one was Buse 2004,[56] excluded from this TAR, because patients had failed on sulphonylurea monotherapy but not had metformin.

The IQWiG review concluded that;

- the reduction in HbA1c was comparable for exenatide and insulin
- no difference in the frequency of severe hypoglycaemia was shown in the trials against insulins
- patients on exenatide lost weight, but those on insulin gained weight.
- the long-term benefits or harms of exenatide are unclear.

2.5.1 Post-prandial hyperglycaemia

The slowing of gastric emptying by the incretin mimetics could in theory reduce post-prandial hyperglycaemia.

2.5.2 Acute pancreatitis

There have been recent concerns about acute pancreatitis in people treated with exenatide.[88] The FDA had (as at end of 2006) reviewed 30 reports of acute pancreatitis in patients on exenatide. Nearly all had other possible reasons for pancreatitis, including

gallstones and alcohol use. Nearly all improved after exenatide was stopped, and a few in whom it was started again had a recurrence of symptoms. However the improvement after the drug was stopped may be coincidental. The FDA has asked for a warning to be added to patient information, has arranged enhanced monitoring, but has not restricted use.[89]

The MHRA (Drug safety Update May 2008)[90] has called for vigilance. It notes that by September 2007, there had been 89 reports of acute pancreatitis, with, curiously, 87 in the USA and two in Germany. One case has since been reported in the UK, after only 5 μg of the drug.

2.6 Summary

In patients with inadequate control, the addition of exenatide led to a fall in HbA1c of about 1.0%. In trial against insulins, the HbA1c results were comparable. There was less nocturnal hypoglycaemia with exenatide than with insulin. In trials against insulin, patients on exenatide lost weight whereas those on insulin gained weight. Nausea is very common, especially initially, but is not usually severe.

The need to inject exenatide twice daily may be a deterrent, but a long-acting once-weekly form is coming.

3 Chapter 3: The DPP-4 inhibitors.

This chapter draws on the recently published Cochrane review by Richter and colleagues[91], but focuses on the comparisons which are relevant to this guideline.

As mentioned in the previous chapter, naturally occurring GLP-1 is broken down by the enzyme DPP-4. DPP-4 inhibitors or “gliptins” prevent GLP-1 degradation and prolong its half life. Two inhibitors are currently on the market, vildagliptin and sitagliptin, both for once daily oral administration. A third, saxagliptin, is coming. The manufacturer has submitted a request for regulatory approval to the FDA.92 A new drug application (NDA) for a fourth drug, alogliptin (Takeda Pharmaceutical), was submitted in 2007. However Takeda has recently been notified by the FDA that the cardiovascular safety data that it is in the process of reviewing for alogliptin are "insufficient." The announcement is expected to delay approval of the drug.

3.1 Methods

For the review of the clinical effectiveness of the DPP-4 inhibitors, the primary sources of evidence were systematic reviews of RCTs, and recent RCTs, with other types of study such as open label extensions being used only for data on duration of effect, side-effects and continuation rates. Because the Cochrane review by Richter and colleauges[91] is very recent, we searched only for studies which had been published after the searches for the Cochrane review were done.

Types of interventions

Treatment for a minimum of 12 weeks with DPP-4 inhibitors (sitagliptin or vildagliptin) in combination with meglitinide analogues, metformin, a sulphonylurea or a thiazolidinedione.

As with the GLP-1 analogues, the comparisons of interest for this review are based on the licensed indications, and on the standard treatment of type 2 diabetes, as set out in the NICE guideline (2008)[6], the algorithm from which was reproduced in the previous chapter.

The licensed indications are as follow.[93]

Sitagliptin

- in patients with type 2 diabetes, to improve glycaemic control in combination with metformin when diet and exercise plus metformin, do not provide adequate glycaemic control
- in combination with a sulphonylurea, in patients who cannot tolerate metformin, or in whom metformin is inappropriate, when maximally tolerated dose of a sulphonylurea does not provide adequate control
- for patients with type 2 diabetes in whom use of a thiazolidinedione is appropriate, sitagliptin is indicated in combination with the PPAR agonist when diet and exercise alone do not provide adequate glycaemic control.
- To improve glycaemic control in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control

This differs from the FDA approval[94] which allows monotherapy as well.

Vildagliptin is indicated in the treatment of type 2 diabetes, as dual oral therapy in combination with:

- metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin

- a sulphonylurea, in patients with insufficient glycaemic control despite maximum tolerated dose of a sulphonylurea and in whom metformin is inappropriate due to contraindications or intolerance
- a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

The following comparisons are relevant to this review.

Comparison 1 – when dual therapy with metformin (or a glitazone) and a sulphonylurea have failed to achieve adequate control.

The main comparisons will be;

- metformin + sulphonylurea versus metformin + either DPP-4 inhibitor
- sulphonylurea + glitazone versus sulphonylurea + either DPP-4 inhibitor
- sulphonylurea + glitazone versus glitazone + either DPP-4 inhibitor
- metformin + glitazone versus metformin + either DPP-4 inhibitor
- metformin + sulphonylurea versus metformin + sulphonylurea + sitagliptin

Comparison 2 – as an alternative to adding insulin to oral therapy

This would be in patients who have failed to achieve adequate control on dual or triple oral therapy. In those starting insulin, it is assumed that metformin would be continued, so the comparisons include;

- metformin + long-acting insulin versus metformin + a DPP-4 inhibitor

Comparison 3

There is evidence that in patients failing on standard combination therapy, an intensive lifestyle intervention (diet and supervised exercise) can be as good as starting insulin. So it may be that rather than start a DPP-4 inhibitor, an intensive lifestyle package could be tried.

- dual therapy + lifestyle versus dual therapy + a DPP-4 inhibitor

3.2 Exclusions

- trials of DPP-4 monotherapy versus placebo. These can show that the DPP-4 inhibitors are pharmacologically active, but are not relevant to standard practice.
- trials of DPP-4 monotherapy versus monotherapy with other oral agents – not relevant to standard practice.
- trials of DPP-4 inhibitors in combination with insulin (not licensed)

The Cochrane review of the DPP-4 inhibitors found 29 comparisons (some of the 25 trials had more than one arm), but these included;[91]

- six trials of sitagliptin monotherapy versus placebo
- two trials of sitagliptin monotherapy versus metformin or glipizide
- four trials of a sitagliptin combination versus metformin monotherapy
- one trial of a sitagliptin combination versus pioglitazone monotherapy
- one trial of a sitagliptin combination versus glimepride monotherapy
- two trials of a sitagliptin combination versus alternative dual therapy
- six trials of vildagliptin monotherapy versus placebo
- three trials of vildagliptin monotherapy versus metformin, pioglitazone or rosiglitazone monotherapies

- two trials of vildagliptin and metformin versus metformin monotherapy
- two trials of vildagliptin and pioglitazone versus piogliatzone alone
- one trial of vildagliptin and insulin versus insulin alone
- one trial of vildagliptin and metformin versus pioglitazone and metformin.

About half of all the vildagliptin trials were in patients who had never had an oral drug, but had been treated only with diet and exercise.

Most of these studies from the Cochrane review are not relevant to this review. Table 9 shows which studies from the Cochrane review are exclusions for this HTA report, and the reasons.

Table 9: Trials, or arms of trials, of DPP-4 inhibitors excluded from this review.

Study	Reason for exclusion
Ahren 2004 [95]	Compared with metformin monotherapy
Aschner 2006 [96]	Compared to placebo
Bosi 2008 [97]	Compared to metformin monotherapy
Charbonnel 2006 [98]	compared to metformin monotherapy
Dejager 2007 [99]	Compared to placebo
Fonseca 2007 [100]	compared to metformin monotherapy
Garber 2007 [101]	compared to pioglitazone monotherapy
Goldstein 2007 a [102]	Compared to placebo
Goldstein 2007 b [102]	Compared with metformin monotherapy
Hanefeld 2007 [103]	Compared to placebo
Mimori 2006 [104]	Compared to placebo
Nonaka 2008 [105]	Compared to placebo
Pan 2008 [106]	Compared to acarbose monotherapy
Pi-Sunyer 2007 [107]	Compared to placebo
Pratley 2006 [108]	Compared to placebo
Raz 2006 [109]	Compared to placebo
Raz 2008 [110]	Compared with metformin monotherapy
Ristic 2005 [111]	Compared to placebo
Rosenstock 2006 [112]	compared to pioglitazone monotherapy
Rosenstock 2007a[113]	compared to rosiglitazone monotherapy
Rosenstock 2007b [114]	compared to pioglitazone monotherapy
Rosenstock 2008 [115]	Compared to placebo
Scherbaum 2008 [116,117]	Compared to placebo
Schweizer 2007 [118]	Compared with metformin monotherapy
Scott 2007a [119]	Compared to placebo
Scott 2007b [120]	Compared to placebo

What do the excluded studies tell us?

Compared to placebo, sitagliptin and vildagliptin reduced HbA1c by around 0.7 % and 0.6% respectively. The sitagliptin versus placebo trials demonstrated substantial heterogeneity. (However, after eliminating a single study of Japanese patients only, Cochrane review noted that the heterogeneity decreased to an I2 value of 25%). There was no weight loss advantage with the DPP-4 inhibitors.

Compared to monotherapy with other agents, neither drug showed any advantage.

There are no data on diabetic complications or mortality, but that is to be expected because of the short duration. Most included trials were 24 weeks duration Three were for 52 weeks.

The trials gave no data on costs or quality of life.

Both drugs were well-tolerated. No severe hypoglycaemia was reported.

3.3 Inclusions

A disappointingly small number of trials met our inclusion criteria – only four. All were funded by the manufacturers, and half or more of the authors were from the manufacturer.

The characteristics of the included trials are shown in Appendix 3

There were no trials for comparisons 1b and 1c.

Comparison 1a

Nauck 2007: sitagliptin + metformin versus glipizide + metformin

This 52-week trial[121] recruited 1172 patients, mean age 57 years and mean duration six years, whose control was unsatisfactory (HbA1c 6.5% to 10%) on metformin alone. They had a period of dose titration on metformin first. They were randomised to sitagliptin (100mg once daily) or glipizide (starting dose 5mg/day). The latter was titrated up aiming at a target for pre-meal blood glucose of under 6.1 mmol/l, but could be reduced if hypoglycaemia was a problem. It was designed to confirm non-inferiority of sitagliptin to glipizide, and did so.

Comparison 1d

Bolli 2008: vildagliptin + metformin versus pioglitazone + metformin

This 24 week trial[122] recruited 576 patients whose control was inadequate (HbA1c 7.5 to 11%) on metformin alone, and randomised them to additional vildagliptin or additional pioglitazone, in a 24-week trial. Participants had poor control (Hba1c 7.5 to 11%), were aged 18 to 77 (mean about 57 years), and had had diabetes for a mean of 6.4 years. It showed that vildagliptin was not inferior to pioglitazone.

Scott 2007: sitagliptin + metformin versus rosiglitazone + metformin

This 18-week trial[120] also recruited 273 patients whose control was inadequate on metformin monotherapy, and randomised them to dual therapy with either sitagliptin or rosiglitazone, or to a placebo group having metformin monotherapy. Patients were 18 to 75 years of age, taking at least 1500 mg of metformin each day. Inadequate control was defined as HbA1c of 7% or over (but not more than 11%). The average duration of diabetes was 5 years (range 0.2 to 19 years). After 18 weeks, the mean HbA1c levels decreased by 0.22% in the placebo arm, and by 0.73% and 0.79% in the sitagliptin and rosiglitazone arms respectively. So the net gain in HbA1c from sitagliptin over placebo was 0.51%. There was weight gain with rosiglitazone (1.5kg) but reductions with sitagliptin (0.4kg) and placebo (0.9kg).

Comparison 1e

Hermansen 2007: sitagliptin + glimepiride + metformin versus glimepiride + metformin

There were four arms and 441 patients in this 24 week trial[123] the two above, a glimepride monotherapy arm, and a sitagliptin + glimepiride arm (a combination not currently licensed in Europe). The mean age at entry was around 57, and the mean duration of diabetes was around 8.5 years. They had inadequate control (HbA1c of 7.5% or over, up to 10.5%) on a sulphonylurea alone or with metformin. Mean baseline HbA1c was 8.34%. Sitagliptin 100mg

once daily reduced HbA1c by 0.89% compared to placebo, in patients also treated with both glimepride and metformin.

There were no trials for comparisons 2 and 3.

3.3.1 Quality of included trials

The quality of the included trials, as shown in Table 10, was good.

Table 10: Quality of DPP-4 studies

Study	Method of randomisation	Allocation concealment	Blinding	ITT analysis	% completed	Power calculation	Similarity at baseline	Sponsorship by manufacturer
Bolli 2008	Not reported. 295 allocated to vildagliptin arm vs 281 to pioglitazone	Not reported	Double blind	Per protocol	89% and 87%	Yes	Good	Funded by Novartis and corresponding author from company
Hermansen 2007	Computer generated	Yes	Double blind	No	92/113 and 102/116	yes	Good	Funded by Merck and 4/6 authors from company
Nauck 2007	Not reported	Not reported	Not blinded	No – per protocol	67% and 74%	Not clear	Good	Funded by Merck with four authors from company
Scott 2007	Not reported	Not reported	Double blind	Per protocol	90% and 98%	Not clear	Good	Funded by Merck and 3/4 authors from company

3.3.2 HbA1c results

Table 11: Summary HbA1c results in DPP-4 trials

Study	Study Arm	HbA1c (%) baseline	HbA1c (%) End	Change from baseline (%)	Difference between groups at end (DPP-4 inhibitor - Comparator)	P value between groups	% achieving Hba1c <7%
Bolli 2008	Vildagliptin + metformin	8.4%		- 0.88% (+/- 0.5%*)	0.10% (95% CI – 0.05 to -0.26)		27%
	Pioglitazone + metformin	8.4%		- 0.98% (+/-0.06%*)			36%
Hermansen 2007	Sitagliptin + metformin + glimepiride	8.27%		-0.59%	-0.89	<0.001	22.6%
	Metformin + glimepiride	8.26%		+ 0.30%			1.0%
Nauck 2007	Sitagliptin + metformin	7.7% (all)	6.86% (PP)	- 0.67%	- 0.02	NS	63%
	Glipizide + metformin	7.6%	6.84%	- 0.67%			59%

Study	Study Arm	HbA1c (%) baseline	HbA1c (%) End	Change from baseline (%)	Difference between groups at end (DPP-4 inhibitor - Comparator)	P value between groups	% achieving Hba1c <7%
Scott 2007	Sitagliptin + metformin	7.8%	7.01%	- 0.79%	+ 0.07	NS	55%
	Rosiglitazone + metformin	7.7%	6.94%	- 0.76%			63%

** Standard Errors as reported by authors. The different sized SEs look odd. It may be the 0.5% for the vildagliptin group which is wrong – it looks that way from the graph of HbA1c in the paper. It should perhaps be 0.05%?*

The results for Hba1c in Table 11show that sitagliptin and vildagliptin have similar effects to a glitazone, but an improvement of 0.9% compared to placebo.

3.313 Weight change

Table 12: Weight changes in DPP-4 trials

Study	Study arm	BMI baseline	Weight – kg (SD) baseline	Change from baseline (%)	Difference between groups at end (DPP-4 inhibitor-Comparator)	P value between groups
Bolli 2008	Vildagliptin + metformin	32.2	91.8 (18.5)	0.3kg	-1.6kg	< 0.001
	Pioglitazone + metformin	32.1	91.2 (16.9)	1.9kg		
Hermansen 2007	Sitagliptin + metformin + glimepiride	31.3	87.2 (19.7)	+ 0.4kg	+ 1.1 kg	
	Metformin + glimepiride	30.7	86.7 (21.1)	- 0.7kg		
Nauck 2007	Sitagliptin +metformin	31.2	89.5	-1.5kg	- 2.6 kg	< 0.001
	Glipizide + metformin	31.3	89.7	+ 1.1kg		
Scott 2007	Sitagliptin + metformin	30.3	83.1 (17.1)	- 0.4kg	- 1.9kg (95% CI 1.3 to 2.5)	
	Rosiglitazone + metformin	30.4	84.9 (18.5)	+1.5kg		

Table 12 show there was less weight gain than with the glitazones (Bolli 2008 and Scott 2007), but that is mainly because people on glitazones gained weight, not because those on a DPP-4 inhibitor lost any. In the comparison with glipizide, the sitagliptin arm ended 2.6 kg lighter. In the Hermansen trial there was more weight gain with the DPP-4 inhibitor than the placebo control arm.

The Cochrane review concluded (see tables 13 and 14 in under “Additional tables” for details) that in trials against placebo, there was greater weight loss after placebo treatment than with sitagliptin and vildagliptin. The pooled estimate for sitagliptin studies was a weighted mean difference of 0.7 kg (95% CI 0.3 to 1.1, P = 0.0002) in favour of placebo and 0.8 kg (95% CI 0.2 to 1.3, P = 0.009), for vildagliptin studies in favour of placebo. Most active hypoglycaemic comparators also resulted in more pronounced weight losses than sitagliptin or vildagliptin treatment.

So the DPP-4 drugs do not seem to have as great a weight reduction effect as exenatide, but in most cases, there is no weight gain, which compared to sulphonylureas and glitazons, is an advantage.

3.314 Adverse events

Table 13 shows selected adverse events.

Table 13: Adverse Events in DPP-4 trials

Study		Nausea	Vomiting	Diarrhoea	Other Gastro-intestinal	Any Adverse Event	Discontinuation due to side effects
Bolli 2008	Vildagliptin + metformin	NR	NR	3.4%	3.1% (constipation)	2.0%	3.1%
	Pioglitazone + metformin	NR	NR	2.9%	1.1 % (constipation)	4.6%	3.2%
Hermansen 2007	Sitagliptin + metformin + glimepiride	0.9%	1.7% (2 patients ex 116)	0.9%	All GI AEs 4.3%	18%	1.7%
	Metformin + glimepiride	0.9%	0.9% (1 patient ex 113)	3.5%	All GI AEs 7.1%	7.1%	1.8%
Nauck 2007	Metformin + sitagliptin	2.6%	0.4%	5.8%	2.7% (abdominal pain)	71%	2.7%
	Metformin + glipizide	2.7%	1.5%	5.5%	2.1%	76%	3.6%
Scott 2007	Sitagliptin + metformin	1%	1%	3%	Any GI 9%	39%	2%
	Rosiglitazone + metformin	1%	1%	3%	Any GI 7%	44%	0%

For full details, see Tables 15 to 27 of the Cochrane review by Richter and colleagues. As mentioned above, the drugs were well tolerated. Discontinuation due to adverse effects did not differ significantly between sitagliptin or vildagliptin intervention and control arms. The risk ratios of serious adverse events also did not show statistically significant differences between groups.

In the Cochrane review, headache was reported more often with DPP-4 inhibitors, especially following vildagliptin therapy.

3.3.5 Hypoglycaemia

Bolli and colleagues defined hypoglycaemia as symptoms suggestive of low blood glucose, confirmed by self-monitored glucose under 3.1 mmol/l plasma glucose. Hypoglycaemia was reported in only one patient in the Bolli study, in the vildagliptin group, and it was mild.

In the Hermansen trial, any hypoglycaemia was reported in 16% of the sitagliptin group versus 0.9% of the control group. In the Scott study, hypoglycaemia was reported in 1% of both groups. No severe hypoglycaemia was reported.

Nauck and colleagues defined severe hypoglycaemia as requiring medical assistance, and had another category where non-medical assistance was sufficient. Any hypoglycaemia was reported in 32% in the glipizide arm and in 5% in the sitagliptin arm severe hypos were reported in 1.2% and 0.2% respectively. Hypoglycaemia of the “non-medical assistance needed” category were reported in 1.4% (8 patients) and 0.2% (one patient).

In the wider Cochrane review by Richter and colleagues, severe hypoglycaemia was not reported in patients taking sitagliptin or vildagliptin, and there were no statistically significant differences in hypoglycaemic episodes between sitagliptin/vildagliptin and comparator groups

3.3.6 Infections

The Cochrane review by Richter and colleagues reported an increase in all-cause infections.

The Merck & Co responses to the consultation mentioned the analysis by Williams-Herman and colleagues (who are from Merck),[124] and stated that this did not find any increase in infections.

There are three reviews which report infection rates in DPP-4 inhibitor trials.

The Cochrane review by Richter and colleagues[91] included all RCTs in adults with type 2 diabetes, with trial duration of at least 12 weeks. It included 25 trials: 11 sitagliptin; 14 vildagliptin. Study duration ranged from 12 to 52 weeks. Searches were done until Jan 2008.

All-cause infections (for example nasopharyngitis, upper respiratory tract infection, urinary tract infection) showed a statistically significant increase after sitagliptin treatment (RR 1.29, 95% CI

1.09 to 1.52, P = 0.003) but did not reach statistical significance following vildagliptin (RR 1.04, 95% CI 0.87 to 1.24, P = 0.7) therapy.

A review by Amori and colleagues[32] also included RCTs of at least 12 weeks duration. Searches were until May 20, 2007. They found 8 sitagliptin studies and 12 vildagliptin studies.They found a slightly increased risk of nasopharyngitis (6.4% for DPP-4 inhibitor vs 6.1% for comparator; risk ratio, 1.17; 95% CI, 0.98-1.40), which was significant only for sitagliptin (RR 1.38, CI 1.06 to 1.81). The risk of urinary tract infection (UTI) was increased by about 50% (3.2% for DPP-4 inhibitor vs 2.4% for comparator; risk ratio, 1.5; 95% CI, 1.0-2.2), and this was seen with both DPP-4 inhibitors, though in the individual comparisons, confidence intervals on risk rations were wide and overlapped with unity.

Amori and colleagues accepted that the relative risks were small, but commented;

"there are more than 20 million patients with diabetes in the United States who are both more likely to develop a urinary tract infection and are at higher risk of complications, including death from urosepsis. A relative risk of 1.5 increases the number of urinary tract infections by 1 million newcases per year, placing a significant burden on the individual patient and the health care system. Until more safety data are available, it may be prudent to avoid use of these agents in patients with a history of recurrent urinary tract infections."

The analysis by Williams-Herman and colleagues[124] included sitagliptin (100mg dose) only. It pooled 12 large phase 2b and 3 RCTs, with duration at least 18 weeks (up to two years), based on data available in the industry database at November 2007. They reported that the only infection more common in the sitagliptin group was nasopharyngitis, with 7.1% in the sitagliptin group versus 5.9% in the comparators, but that the 95% CI for the difference overlapped with no difference (95% CI from -0.1 to + 2.4). They found no difference in the frequency of UTIs.

So we have two independent reports suggesting an increase in UTIs, and the manufacturer's analysis reporting no increase.

The attached table shows the trials included in these reviews.

Study ID	Richter 2008	Amori 2007	Williams-Herman 2008	Vildagliptin or Sitagliptin
Ahren 2004 [95]	✓	✓	NA	V
Aschner 2006 [96]	✓	✓	✓	S
Bolli 2008 [122]	✓	×	NA	V
Bosi 2007 [97]	✓	✓	NA	V
Charbonnel 2006 [98]	✓	✓	✓	S
Dejager 2007 [99]	✓	✓	NA	V
Dobs 2008 [125]	×	×	✓	S
Fonseca 2007 [100]	✓	✓	NA	V
Garber 2007 [101]	✓	✓	NA	V
Goldstein 2007 [102]	✓	×	✓	S
Hanefeld 2005 [126]	×	✓	×	S
Hanefield 2007 [103]	✓	×	✓	S
Hermansen 2007 [123]	✓	×	✓	S
Mimori 2006 [104]	✓	✓	NA	V
Nauck 2007 [121]	✓	✓	✓	S
Nonaka 2008 [105,127]	✓	✓	×	S
Pi-Sunyer 2007 [107]	✓	✓	NA	V
Pratley 2006 [108]	✓	✓	NA	V
Raz 2006 [109]	✓	✓	×	S
Raz 2008 [110]	×	×	✓	S
Ristic 2005 [111]	✓	✓	NA	V
Rosenstock 2006 [112]	✓	✓	✓	S
Rosenstock 2007b [113]	✓	✓	NA	V
Rosenstock 2007a [114]	✓	✓	NA	V
Scherbaum 2008 [117,128]	✓	×	NA	V
Schweizer 2007 [118]	✓	✓	NA	V
Scott 2007a [119]	✓	✓	✓	S
Scott 2007b [120]	✓	×	×	S

Study ID	Richter 2008	Amori 2007	Williams-Herman 2008	Vildagliptin or Sitagliptin
Yang 2007 [129]	×	×	✓	S
P023 (Merck & Co, unpublished)	×	×	✓	S

✓ = trial included; × = trial not included

3.3.7 Quality of life

No publication provided data on health-related quality of life.

3.3.8 Hypothetical adverse effects.

In addition to reducing the breakdown of the incretins, GLP-1 and gastric inbitory peptide (GIP), DPP-4 inhibitors also prolong the action of a number of neuropeptides, like neuropeptide Y, growth hormone-releasing hormone and chemokinines, such as stromal-cell derived factor 1 and macrophage-derived chemokine. Potential side-effects include neurogenic inflammation, increase in blood pressure, enhanced inflammation and allergic reactions. DPP-4 contributes to T-cell activation, raising the possibility that these compounds compromise immune function.[130] Levels of tissue DPP-4 are reduced in nasal tissue of people with chronic rhinosinusitis and DPP-4 inhibition seems to aggravate nasopharyngitis as could be observed in clinical studies.

Therefore, the long-term safety of DPP-4 inhibitors merits further investigation, and it seems to be important to monitor DPP-4 treated patients for the development of inflammatory conditions, such as angioedema, rhinitis and urticaria.

3.3.9 Costs

Both the sitagliptin trials used 100 mg daily, which at a cost (BNF 55[131]) of £33.26 for 28 tablets, comes to £432 a year.

No cost is available for vildagliptin yet. The dose used by Bolli and colleagues was also 100 mg daily.

3.3.10 Beta-cell function

A progressive reduction in beta-cell mass contributes significantly to gradual loss of glycaemic control in individuals with type 2 diabetes. A major goal of diabetes research is to restore the beta-cell mass typically lost during the natural progression of type 2 diabetes. Current treatments not only show no ability to reduce beta-cell loss, but some such as the sulfonylureas have been shown to induce beta-cell apoptosis in cultured human islets.[132] If the DPP-4 inhibitors can enhance beta-cell survival and stimulate beta-cell growth, they may provide a means to preserve or restore functional beta-cell mass in individuals with type 2 diabetes.

The Cochrane reviewers found few data on measurements of beta-cell function, especially for vildagliptin.[91] The variety of methods used also made definite conclusions on the effects of DPP-4 inhibitors on beta-cell function difficult. Inspection of the sitagliptin homeostasis model assessment beta (HOMA-beta) data seems to indicate that sitagliptin compared to placebo results in increased values of beta-cell function measurements, but the effect in comparison with other hypoglycaemic agents does not seem to be clear-cut.

Most studies are quite short. An exception is the two year extension study by Scherbaum and colleagues (2008).[116] This study (funded by Novartis, with the corresponding author from the company) was one of our exclusions because it compared vildagliptin only with placebo, but it does provide some data on a measure of beta –cell function, the insulin secretory rate

relative to glucose level after meals. This measure reflects the responsiveness of the beta cell to glucose, rather than absolute insulin production or plasma insulin level. The extension study was done in under half of those who completed the original study (108 compared to 264). All of the original recruits had HbA1c in the range 6.2% to 7.5%. At recruitment the mean duration was 2 years.

Scherbaum and colleagues found that their measure of insulin secretory rate (ISR)/glucose "tended to increase" from end of year 1 to end of year 2, by which they mean that there was an increase which did not reach statistical significance. The implication is that there may be a steady improvement in beta cell function. However, the mean HbA1c in the vildagliptin group fell after initiation, reached a nadir of about 6.2% by around 32 weeks, and then slowly rose to about 6.4% by 110 weeks. That rise suggests that vildagliptin is not having a dramatic effect on beta cell function. It may be slowing the progression of the disease which has been reported by the UKPDS (16 or 17).[4,5] It is worth noting that the graph shows that mean HbA1c rose a little more steeply in the placebo group, whereas in UKPDS the lines were roughly parallel

So far, no definite conclusions can be drawn on the effects of sitagliptin and vildagliptin on long-term beta-cell function. If beta cell function does improve, and if that improvement is sustained over the long term (say 10 to 20 years), then that would be very important, and there would be a case for early use, perhaps as the first drug to be used when diet fails. Or given that diet usually fails, perhaps from diagnosis of type 2 diabetes.

There could be an issue about the duration of diabetes at which any beta cell preservation effect might be seen. The UKPDS study reported that at diagnosis, about half of beta cell function had been lost.2 If patients are then treated with incretin enhancers or mimetics after they had had diabetes for many years, it may be too late to see much effect. It would be interesting to assess effects on beta cell function by duration of known diabetes. And perhaps also in people with impaired glucose tolerance (there is one trial of the effects of a DPP-4 inhibitor on people with impaired glucose tolerance[115]).

3.3.11 Emerging studies.

Another third-line trial was reported at the ADA 2008 conference, in abstract only, by Dobs and colleagues.[125] It was an 18 week RCT of adding sitagliptin to metformin and rosiglitazone. HbA1c fell by 0.7% overall, but by 1.3% in those whose baseline HbA1c was over 9%.

At the same meeting, Krobot and colleagues had an abstract [133] from a second-line trial, of metformin and sitagliptin versus metformin and glipizide. The effects on HbA1c were similar, but hypoglycaemia was less frequent with sitagliptin (any hypoglycaemic event 5%) than the sulphonylurea (32%).

At the 2008 conference of the European Association for the Study of Diabetes (EASD) in September, three new gliptin trials were presented. One by Goodman and colleagues[134] was of vildagliptin versus placebo as an add-on to metformin, and would be an exclusion under our criteria.

The other two are of interest. Arjona-Ferreira and colleagues[135] describe a Merck-funded trial of adding sitagliptin in patients with inadequate control (HbA1c 7.5 to 11%) on metformin and rosiglitazone. Adding sitagliptin reduced HbA1c by 0.7% overall, but by 1.3% in those with baseline HbA1c over 9%.

Braceras and associates[136] presented a Novartis trial comparing vildagliptin to a glitazone in patients not adequately controlled (initial HbA1c over 7%) on metformin, and found them to be roughly equivalent. HbA1c fell by 0.68% on vildagliptin + metformin and by 0.57% on glitazone + metformin.

Another new trial[117] was published in full in August 2008, but is not relevant for our purposes. It compared vildagliptin and placebo in patients who had not previously had drug treatment. Their hyperglycaemia was mild (baseline HbA1c 6.2 to 7.5%). After a year on treatment, HbA1c fell by 0.3% on vildagliptin and rose by 0.15% on placebo, which was statistically significant, if not clinically so. It does provide a useful reminder that the size of reduction in HbA1c depends on baseline level.

3.4 Conclusions

Sitagliptin and vildagliptin are clinically effective in reducing blood glucose, do not cause problems with hypoglycaemia, and are well-tolerated. However we cannot yet say what the long-term effects on diabetes complications will be, nor what long term adverse effects may appear.

Only indirect comparisons can be made with the GLP-1 analogues, because there have been no head to head trials. The main differences are that the DPP-4 inhibitors are given orally, are less expensive, cause fewer adverse events in the short term, but may be slightly less potent in lowering blood glucose, and do not cause weight loss. They may not be so specific in action, and their effects on the immune system require monitoring.

4 Chapter 4 The long-acting insulin analogues.

4.1 Objectives

In this chapter, we assess the effects of the new insulin analogues, glargine and detemir with older long-acting (e.g. ultralente) and intermediate acting insulins (e.g. NPH).

4.1.1 Background

An ideal basal insulin would have a flat action profile (i.e. the same level at all times of day) with no day to day variability in the same patient. Older long-acting insulins used a crystalline or amorphous suspension, that formed a slowly dissolving depot after subcutaneous injection. The newer longacting analogues have adopted different approaches. Both have structural changes.

In glargine, these changes mean that it is soluble in the acidic (pH 4.0) solvent in which is it provided, but once injected into the neutral pH of the subcutaneous tissues, it forms stable hexamers which slowly release the insulin into the blood stream.[137] In detemir, one amino acid is omitted and a long-chain (14-carbon) fatty acid, myristoyl, is attached. This facilitates binding of detemir to serum albumin. It has been suggested[138] that albumin binding may facilitate transport into the brain, and that this might cause slightly less weight gain than is seen with other insulins.[139]

4.2 Methods

4.2.1 Inclusion criteria

4.2.1.1 Types of studies

A number of high quality systematic reviews already exist in this area, so in the first instance, we reviewed systematic reviews of randomised controlled trials (RCTs). The reviews had to include at least one RCT of at least 12 weeks duration. We also considered any additional RCTs published after the last search of any relevant included review. The trials had to have a minimum duration of 12 weeks, although trials of at least 24 weeks' duration were preferred.

4.2.1.2 Types of participants

Patients of any age and gender with type 2 diabetes.

4.2.1.3 Types of interventions

In type 2 diabetes, treatment with insulin is started when control on a combination of oral drugs is unsatisfactory. Therefore the comparators of glargine / detemir were other basal insulins, usually NPH but occasionally ultralente. Metformin will now usually be continued, and other oral therapies may be used. Some trials used insulin alone. So comparisons can include:

1. glargine + oral agents versus NPH + oral agents
2. detemir + oral agents versus NPH + oral agents
3. glargine + oral agents versus ultralente + oral agents
4. detemir + oral agents versus ultralente + oral agents
5. glargine versus detemir

6. glargine or detemir alone versus NPH alone

Overweight people with type 2 diabetes often do not achieve good glycaemic control after switching to insulin, partly because it can cause further weight gain. We set out to review one other option (but did not identify any new relevant trials):

metformin + sulphonylurea + insulin versus metformin + sulphonylurea + lifestyle interventions

The trial by Aas and colleagues[27] (already described in chapter 1) is relevant here.

There are trials of the long-acting analogues against short-acting insulins at meal-times, for example once daily glargine versus thrice daily aspart. We excluded such trials, because they are comparing different approaches to glycaemic control, rather than the new and old basal insulins.

4.2.1.4 Types of outcomes

We planned to consider the following outcome measures:

- HbA1c
- Frequency of hypoglycaemia, especially if severe
- Glycaemic excursions, including post-prandial hyperglycaemia
- Total daily dose of insulin
- Weight gain or loss
- Complication rates – retinopathy, nephropathy, myocardial infarction, angina, heart failure, stroke, amputation, death
- Adverse events
- Health-related quality of life

4.2.2 Search strategy

Relevant literature was identified, and comprehensiveness checked, by:

- Searches of bibliographic databases, Medline, Cochrane Library, and Embase
- Checking reference lists of retrieved studies
- Obtaining lists of published studies from manufacturers
- Our peer review process

Searches were also done to identify emerging evidence, from conference abstracts and trial registers. Studies available only in abstract were included in the assessment of clinical effectiveness if there is a paucity of studies published in full in peer reviewed journals, but they were reported with appropriate caution. Our default position is for studies available only in abstract not to be used.

Authors of previous studies were not contacted.

4.2.3 Quality assessment of studies

The quality of systematic reviews was assessed using the following quality criteria, based on the NICE guidelines manual:

- Appropriate and clearly focused question
- Inclusion and exclusion criteria described
- Literature search sufficiently rigorous to identify all relevant studies
- Study selection described

- Data extraction described
- Study quality assessed and taken into account
- Study flow shown
- Study characteristics of individual studies described
- Quality of individual studies given
- Results of individual studies shown
- Enough similarities between studies selected to make combining them reasonable

Each of the items was rated as: well covered / adequately addressed / poorly addressed / not addressed / not reported / not applicable

The overall quality of the review was rated as (++), (+) or (-).

Randomised controlled trials were assessed on the following criteria based on the NICE guidelines manual:

- Appropriate and clearly focused question
- Method of randomisation
- Allocation concealed
- Participants blinded
- Outcome assessors blinded
- All relevant outcomes measured in standard, valid, reliable way
- Proportion of participants excluded / lost to follow-up
- Handling of missing data
- Intention-to-treat analysis performed
- Statistical analysis appropriate
- Only difference between groups is treatment under investigation
- Results in multi-centre studies comparable for all sites
- Groups comparable at baseline

Again, overall quality of the trials was classified as (++), (+), or (-).

4.2.4 Data extraction

Data extraction was carried out by one researcher and checked by another. Any disagreements were resolved through discussion, involving a third person if necessary.

4.2.5 Data analysis

The clinical effectiveness, relative to the key comparators, was assessed, in terms of difference in effect size. (The key question for the cost-effectiveness analysis is not whether a drug is better than the comparator, but how much better.)

Data were summarised using tables and text. In addition, we performed a meta-analysis of all relevant trial data, combining data from the previous meta-analyses with newly identified trials. Data were summarised for continuous variables (e.g. HbA1c, weight change) as weighted mean differences with 95% confidence intervals using the inverse variance method and a random effects model. For dichotomous variables (hypoglycaemia), data were expressed as relative risks with 95% confidence intervals (for patients with or without hypoglycaemia) and summarised using the Mantel-Haenzsel method and a random effects model. For data already used in previous meta-analyses, data were generally used as given in the meta-analyses, although some double-checking was done with the original papers. Where not given directly, standard deviations were either calculated from standard errors or

confidence intervals, or in case of no measure of variability reported, the average of the standard deviations for the other studies for that outcome measure was used. If the standard deviations were missing for more than half of the studies, meta-analysis was considered not to be reliable and a statistical summary was not presented. Meta-analyses were generally done for end-of-study values except for weight change, as most studies reported data for weight change without giving baseline values. Heterogeneity was assessed using the chi-squared statistic.

We had set out to conduct sensitivity analyses to explore uncertainties in important parameters, and of the impact of hypoglycaemic episodes and the fear of hypoglycaemic episodes on quality of life.

We did not include any indirect comparisons, for two main reasons. Firstly, such comparisons are prone to bias due to confounding variables, which may not all be apparent. Secondly, they are used mainly in technology appraisals, when seeking to decide which of two or more options is better or best. We do not expect the guideline development group will wish to make any recommendations of whether glargine should be used in preference to detemir, or vice versa, because such comparisons would be based partly on cost, which may change. Having two drugs available in each group encourages competition on price.

4.3 Systematic Reviews

4.3.1 Search results

Fourteen papers were identified as potentially relevant systematic reviews. Of these, five fulfilled the inclusion criteria.[140-144] Most of the remainder did not use systematic review methodology, and one was only a protocol for a systematic review (see Table 14). Two further systematic reviews were identified after the completion of the present analysis and these will only be summarised briefly.[145,146]

Table 14: Excluded reviews – long acting insulin analogues

Study	Reason for exclusion
Dailey 2003 [147]	not a systematic review, abstract only
Garber 2007 [148]	not a systematic review
Glass 2008 [149]	not a systematic review
Hemraj 2004 [150]	not a systematic review
Mullins 2007a [151]	not a systematic review
Mullins 2007b [152]	not a systematic review, abstract only
Rašlová 2007 [153]	not a systematic review
Rosenstock 2005 [154]	not a systematic review
Swinnen 2007 [155]	protocol only, no full review

4.3.2 Description of reviews

The characteristics of the included reviews are shown in Appendix 4. Of the five included reviews, the reviews by Duckworth and colleagues (2007)[140] and Wang and colleagues (2003)[143] only had a very limited description of methodology, the review by Horvath and colleagues (2007)[141] was a Cochrane review, and the reviews by Warren and colleagues (2004)[144] and Tran and colleagues (2007)[142] were Health Technology Assessments (one from the UK and one from Canada). Four of the reviews had non-industrial funding, while the review by Duckworth and colleagues (2007) was funded by Sanofi-Aventis.

4.3.3 Inclusion criteria

Only four of the five reviews specified the study design of the studies to be included. The others included randomised controlled trials (or just "clinical trials"), where Warren 2004 specified a minimum duration of 4 weeks, Horvath 2007 of 24 week, and Wang 2003 specified a minimum number of participants of 100. Wang 2003 also included other designs to answer different parts of their review question, but only the clinical efficacy trials are considered here.

Both Health Technology Assessments and the review by Wang and colleagues 2003 included both participants with type 1 and type 2 diabetes. The remaining two reviews were only concerned with participants with type 2 diabetes. The present review only summarises parts of the included reviews that describe patients with type 2 diabetes.

The reviews by Duckworth 2007, Warren 2004 and Wang 2003 focussed on insulin glargine, while the reviews by Horvath 2007 and Tran 2007 reviewed the effects of both insulin glargine and insulin detemir. Comparison treatments were NPH insulin in the study by Duckworth 2007 and Horvath 2007, another long-acting basal insulin in the review by Warren 2004, conventional human insulin or oral anti-diabetic agents in the review by Tran 2007, and comparison treatments were not specified in the review by Wang 2003.

Outcomes that reviews set out to assess included glycaemic control (HbA1c, fasting plasma glucose (FPG)), hypoglycaemia (overall, severe and nocturnal), other adverse events, mortality, cardiovascular morbidity, diabetic late complications, and health-related quality of life.

4.3.4 Trials included in systematic reviews

General. The reviews included reports of 14 individual trials of insulin glargine and two trials of insulin detemir as shown in Table 15

Table 15: Trials included in systematic reviews of long acting insulin analogues

	Duckworth 2007 [140]	Wang 2003 [143]	Horvath 2007 [141]	Tran 2007 [142]	Warren 2004 [144]
previous insulin – glargine versus NPH insulin					
Fonseca 2004 [156-158] (subgroup-analysis of Rosenstock 2001)	✓	✓	✓	✓	✓
Rosenstock 2001 [159]	✓	✓	✓	✓	✓
Yokoyama 2006 [160]			✓		
insulin-naïve, oral antihyperglycaemics – glargine versus NPH insulin					
Eliaschewitz 2006 [161]			✓		
Fritsche 2003 [162]	✓	✓	✓	✓	
HOE 901/2004 Study Investigators Group 2003 [163,164]	✓	✓		✓	✓
Massi Benedetti 2003 [165]	✓		✓		
Meneghini 2005 [166]				✓	
Yki-Järvinen 2000 [137]	✓	✓		✓	✓
Yki-Järvinen 2006 [26,167]	✓		✓	✓	
Raskin 1998 [168]		✓			✓
Riddle 2003 [169]	✓	✓	✓	✓	

	Duckworth 2007 [140]	Wang 2003 [143]	Horvath 2007 [141]	Tran 2007 [142]	Warren 2004 [144]
Rosenstock 2006 [170]				✓	
previous insulin – insulin detemir					
Haak 2005 [171]			✓	✓	
insulin-naïve – insulin detemir					
Hermansen 2006 [172]			✓	✓	
unclear					
Witthaus 2000 [173]		✓			

There was one main trial of insulin glargine considering patients with previous insulin treatment (Rosenstock 2001)[159], whereas the remainder of the glargine trials included previously insulin-naïve patients who had been on oral anti-hyperglycaemic agents before the trial and continued an oral regimen during the trial (either their previous treatment or a new treatment as specified by the trial). Of the remaining glargine trials in patients with previous insulin treatment, the trial by Fonseca 2004[158] was in fact a subgroup analysis of Rosenstock 2001. This trial included both patients using a once daily and a twice daily insulin regimen, and Fonseca 2001[157] considered only the subgroup on a once daily insulin regimen. The trial by Yokoyama 2006[160] used two different insulin regimens – dose titration in the glargine group and an unchanged dose of NPH in the comparison group, which was considered to be an inappropriate comparison in the review by Horvath and colleagues. Although the trial was included in their review, it was not considered in detail and it was not included in any analyses. Of the trials on insulin detemir, one included patients previously on insulin, and the other included insulin-naïve patients.

The individual reviews included between five and nine trials of insulin glargine versus NPH insulin, and two trials of insulin detemir versus NPH insulin. Both reviews assessing insulin detemir included the same trials, while only two trials of insulin glargine were included in all reviews. The reviews summarised data of between around 1400 and around 4700 patients in the included trials.

Design. All included trials were open-label randomised controlled trials and many were described as multi-centre trials. Some trials had a non-inferiority or equivalence design. A number of trials were published as abstracts only (especially in the older reviews). Trial duration was between four and 52 weeks. Most trials came from Europe or North America, two also included data from South Africa, and one was conducted in participants from Latin America. A substantial number of trials was industry-funded.

Trial quality. Trial quality was generally rated as rather poor. Blinding was considered difficult or impossible by most reviews, as insulins glargine and detemir exist as a clear solution while NPH insulin has a milky appearance. The review by Horvath and colleagues stresses the bias that can be introduced by lack of blinding and especially the lack of blinding of outcome assessment, which does not seem to have been mentioned or considered by any of the trials. Horvath and colleagues considered all their included trials to have been of insufficient methodological quality, with poor reporting of randomisation in most trials, adequate allocation concealment in five trials, discontinuation rates of between 1.6 and 10.2% and an intention-to-treat approach in all main analyses. The studies included in the review by Tran and colleagues had a mean Jadad score of 2.4 (out of 5, but blinding being impractical, a perfect score was not possible), with adequate allocation concealment in four trials and intention-to-treat analysis in 90%. Warren and colleagues considered quality assessment to be possible for the two full publications included in their review, which both scored 2 on the Jadad score, with none of them specifying a blinded outcome assessment. The Wang review did not present a formal quality assessment, but suggested that there was inconsistent reporting of mean or adjusted mean changes in primary and secondary efficacy endpoints within and between treatment groups, and that studies were generally statistically underpowered.

Participants. Type 2 diabetes patients included in the reviews had a mean age of between 53 and 62 years. Where reported, between 36 and 49% of participants were female, patients had a mean body mass index (BMI) of between 27 and 35 kg/m2, a diabetes duration of between 8 and 14 years, and a mean baseline HbA1c value of between 7.9 to 9.7%.

Interventions. As mentioned above, there was one main trial of insulin glargine[156-159] and one of insulin detemir[171] in patients on previous insulin therapy without concomitant oral anti-hyperglycaemic agents. In three trials of insulin-naïve patients using oral therapy[26,161,162], the patient's previous oral therapy was stopped and replaced by glimepiride[161,162] or metformin.[26] In the other trials, the previous oral therapy was continued. Oral anti-hyperglycaemic agents included metformin, acarbose, pioglitazone, rosiglitazone, sulphonylurea or other insulin secretagogues or alpha-glucosidase inhibitors. One glargine trial included pre-meal regular insulin[159] and one detemir trial included pre-meal insulin aspart.[171] Most glargine trials compared bedtime glargine with bedtime NPH, but one[162] compared morning glargine with bedtime glargine and bedtime NPH, and in one[159], patients received glargine at bedtime and NPH either once at bedtime or twice, at bedtime and in the morning. One of the detemir trials[171] used detemir or NPH once daily at bedtime or twice daily at bedtime and in the morning, while the other[172] used a twice daily regimen of detemir or NPH. Trials used different dose titration targets, between 4.5 and 7.8 mmol/L for fasting blood glucose, or of 7.0 to 7.5% for HbA1c.

Outcomes. Outcomes reported included HbA1c, FPG, blood glucose profiles, hypoglycaemic episodes (overall, symptomatic, severe, and nocturnal), the percentage of patients reaching the titration target, weight change, mortality, quality of life, and adverse events. None of the trials published diabetes secondary complication rates (although Horvath and colleagues retrieved some unpublished information), and there were no quality of life data (one trial reported on patient satisfaction). Trials were underpowered to assess mortality. Weight change was not systematically reported.

4.3.5 Review quality

The review by Duckworth and colleauges (2007) was of poor quality. Its search strategy was restricted to a PubMed search and English articles only, and no information was given on other methodological procedures such as study selection, quality assessment of trials, data extraction, or data analysis. Inclusion criteria were briefly specified, but only for participants, interventions and outcomes, not for study design.

Both the Cochrane review by Horvath and colleauges (2007) and the Canadian HTA Assessment by Tran and colleauges (2007) were of good quality. Inclusion criteria were well described, as was study selection, quality assessment of trials, data extraction, and data analysis. A comprehensive search was carried out and described in detail. Study flow was shown. Both reviews included a meta-analysis.

The UK HTA Assessment by Warren and colleauges (2004) appears good but had some reporting omissions. Inclusion criteria were well described and the search strategy was very comprehensive. However, it is unclear whether study selection and quality assessment were done in duplicate and data extraction was only done by one reviewer. Study flow was not shown.

The review by Wang and colleauges (2003) was of poor quality. Inclusion criteria were described and the search strategy was adequate. However, study selection, quality assessment, data-extraction and data analysis were not described, nor was study flow shown. Although no details of quality assessment methodology were given, some comments on study quality were made.

4.3.6 Results

Main results are shown in Table 16 and subgroup analyses in

Table 17

Table 16: Main results reported in reviews of long acting insulin analogues

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
all studies – glargine versus NPH insulin				
HbA1c				
Horvath 2007	HbA1c (%) (studies with available data)	4	weighted mean difference 0.1% (95% CI: -0.1, 0.2)	p=NS
	HbA1c (%) (all studies, pooled SD)	6	weighted mean difference 0.00% (95% CI: -0.1, 0.1)	p=NS
Tran 2007	HbA1c (%)	7	meta-analysis weighted mean difference 0.05 (95% CI: -0.07, 0.16)	p=NS; no significant difference for analysis by different co-interventions
hypoglycaemia				
Horvath 2007	severe hypoglycaemia	4	meta-analysis, 6-month studies only Peto odds ratio 0.70 (95% CI: 0.40, 1.23)	p=NS; no significant difference or no statistical information for remaining 3 studies
	symptomatic hypoglycaemia	3	meta-analysis, 6-month studies only relative risk 0.84 (95% CI: 0.75, 0.95)	significantly fewer with glargine, p=0.005; for remaining 4 studies: 3 studies no significant difference, 1 significant in favour of glargine (p<0.02)
	overall hypoglycaemia	1	morning glargine: 74% evening glargine: 68% evening NPH insulin: 75%	p=NS
	nocturnal hypoglycaemia	3	meta-analysis, 6-month studies only relative risk 0.66 (95% CI: 0.55, 0.80)	significantly fewer with glargine, p<0.0001; also significant results for the 3 studies not included in the meta-analysis but reporting on nocturnal hypoglycaemia
Tran 2007	overall hypoglycaemia	6	meta-analysis relative risk 0.89 (95% CI : 0.83, 0.96), NNT 14 (95% CI : 9, 33)	p=0.002; no significant difference for analysis by different co-interventions
	severe hypoglycaemia	4	meta-analysis relative risk 1.09 (95% CI : 0.56, 2.12)	p=NS; no significant difference for analysis by different co-interventions
	nocturnal hypoglycaemia	5	meta-analysis	p<0.0001; no significant difference for

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
			relative risk 0.57 (95% CI : 0.44, 0.74), NNT 8 (95% CI : 6, 11)	analysis by different co-interventions
glycaemic excursions				
Tran 2007	8-point blood glucose profiles	3		generally no statistically significant difference between glucose profiles for glargine versus NPH; pre-dinner values lower in two studies for glargine, and in one study for morning (but not evening) glargine versus evening NPH
total daily dose	not reported			
weight change	not reported			
complication rates				
Horvath 2007	mortality	3	small numbers, no study adequately powered to assess this parameter	
	new development of non-proliferative retinopathy	1	glargine: 8.4% NPH insulin: 14%	p-value not reported
	development of clinically significant macular oedema (of people with no retinopathy)	1	glargine: 1.8% NPH insulin: 2.4%	p-value not reported
	progression of retinopathy by more than 3 stages	2	glargine: 5.9 to 7.5% NPH insulin: 2.7 to 9.1%	p-value not reported for one study, significantly more with glargine in the other study p=0.028
	development of clinically significant macular oedema	1	glargine: 11.2% NPH insulin: 6.5%	p=NS
Tran 2007	mortality	4		none of reported deaths thought to be related to study medication
adverse events				
Horvath 2007	overall adverse events	4		numbers comparable between groups
	serious adverse events	2		numbers comparable between groups
	adverse events possibly	4		numbers comparable between groups

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
	related to treatment			
	patients withdrawing due to adverse events	6		numbers comparable between groups
Tran 2007	adverse events	10		no significant differences in adverse events between glargine and NPH
HR quality of life				
Horvath 2007	Diabetes Treatment and Satisfaction Questionnaire	1	more pronounced improvement of treatment satisfaction reported with glargine versus NPH	p<0.05
previous insulin – glargine versus NPH insulin				
HbA1c				
Duckworth 2007	HbA1c (%)	2	glargine: -0.41% NPH insulin: -0.46% to -0.59%	change in HbA1c similar between groups
	target reached (HbA1c ≤7.0 to ≤7.5; FBG ≤6.7 mmol/L)	2	HbA1c glargine: 18% NPH insulin: 18% FBG glargine: 29.6 to 34% NPH insulin: 24 to 27.1%	similar between groups for both studies
Wang 2003	HbA1c (%)	2	glargine: -0.35% to -0.41% NPH insulin: -0.44% to -0.59%	p=NS in one study, not reported for the other
Warren 2004	HbA1c (%)	2	glargine: -0.35% NPH insulin: -0.44% numbers only reported for one	p=NS for both
	patients reaching target FBG	1	glargine: 29.6% NPH insulin: 27.1%	p=NS
hypoglycaemia				
Duckworth 2007	overall symptomatic hypoglycaemia	2	glargine: 46 to 61.4 % NPH insulin: 60 to 66.8 %	p<0.05 in one study, p=NS in the other
	severe hypoglycaemia	2	glargine: 0 to 0.4% NPH insulin: 2.0 to 2.3%	p=NS

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
	nocturnal hypoglycaemia	2	glargine: 15 to 26.5% NPH insulin: 27 to 35.5%	p<0.05 in one study, p=NS in the other
Wang 2003	≥1 episode of hypoglycaemia	1	glargine: 46.2% NPH insulin: 60.4%	p=0.048
	reported nocturnal hypoglycaemic events	2	glargine: 15.4% to 31.3% NPH insulin: 27.1% to 40.2%	p=NS in one study, p=0.014 in other study
	symptomatic hypoglycaemia	2	glargine: 17.3% to 61.4% NPH insulin: 31.3% to 66.8%	p=NS in 1 study, p=0.002 in the other
	episodes of severe hypoglycaemia	1	glargine: 6.6% (-0.4%) NPH insulin: 10.4% (-2.3%)	p=NS
Warren 2004	symptomatic hypoglycaemia	2	glargine: 6.6 to 17.3% NPH insulin: 10.4 to 31.3%	p=NS in one study, p<0.05 in the other study
	nocturnal hypoglycaemia	2	glargine: 15.4 to 35% NPH insulin: 27.1 to 43.7%	p=NS in one study, p<0.05 in the other study
	severe hypoglycaemia	2	not reported separately	
glycaemic excursions	not reported			
total daily dose				
Warren 2004	insulin use	1	for patients on pre-trial once-daily NPH, slightly more insulin used at trial end than at baseline (no data presented) for patients on pre-trial more than once-daily NPH, people on glargine used slightly less at trial end (reduced by 4.4 U/day) and patients treated with NPH used about the same (no more data presented)	unclear
weight change				
Wang 2003	weight gain	1	glargine: +0.4 kg NPH insulin: +1.4 kg p<0.001, CIs not reported	
complication rates				

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
adverse events				
Wang 2003	injection site pain	1	28 weeks greater number of patients reported injection site pain with insulin glargine compared with NPH insulin (pain usually mild and did not result in discontinuation of treatment)	
Warren 2004	injection site pain	1	glargine: 10.4% NPH insulin: 7.7%	unclear, probably p<0.05; but mild and no drop-outs as a result
	insulin antibodies	1	no increases in either comparison group	
HR QoL	not reported			
insulin-naïve, oral antihyperglycaemics – glargine versus NPH insulin				
HbA1c				
Duckworth 2007	HbA1c (%)	5	glargine: -0.46 to -2.36% NPH insulin: -0.38 to -2.44%	4 trials HbA1c similar between groups, 1 trial significantly more HbA1c reduction with morning glargine than bedtime NPH (p<0.001) and with morning glargine versus bedtime glargine (p=0.009)
	target reached (HbA1c ≤7.0 to ≤7.5; FBG ≤6.7 mmol/L)	4	HbA1c glargine: 33 to 58% NPH insulin: 32 to 57.3% FBG glargine: 40.7 to 42% NPH insulin: 35.1 to 44%	3 trials no significant difference, 1 trial significantly more patients reaching target with morning glargine than with bedtime glargine or NPH (p<0.05)
Wang 2003	HbA1c (%)	4	glargine: -0.76% to -1.64% NPH insulin: -0.66 to -1.63%	3 trials no significant difference between glargine and NPH, 1 trial significantly more HbA1c reduction with morning glargine than bedtime NPH (p<0.001) and with morning glargine versus bedtime glargine (p=0.009)
	target reached (≤7.0% to <8.0%)	2	glargine: 53.8 to 57.9% NPH insulin: 43.9 to 57%	1 study p=NS, 1 study unclear

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
Warren 2004	HbA1c (%)	3	glargine: -0.8% NPH insulin: -0.8% numbers only reported for one	p=NS for all studies
	patients reaching target FBG	1	glargine: 7.7% NPH insulin: 7.6%	p=NS
hypoglycaemia				
Duckworth 2007	overall symptomatic hypoglycaemia	6	glargine: 18.8 to 56%, 5.5 to 13.9 events/patient-year NPH insulin: 32.4 to 58%, 8.0 to 17.7 events/patient-year	p<0.05 in 4 studies, p=NS in 2 studies
	severe hypoglycaemia	2	glargine: 0 to 2.5% NPH insulin: 0 to 1.8%	p=NS
	nocturnal hypoglycaemia	5	glargine: 7.3 to 23%, 4.0 events/patient-year NPH insulin: 19.1 to 38%, 6.9 events/patient-year	p<0.05 in all studies
Wang 2003	hypoglycaemic episodes (%)	2	glargine: 7.3% to 33% NPH insulin: 19.1% to 43%	p<0.05 for both studies
	nocturnal hypoglycaemia	3	glargine: 9.9 to 47% NPH insulin: 24 to 55%	p<0.05 for all studies
	Achieving HbA1c ≤7.0%without nocturnal hypoglycaemia	1	glargine: 33% NPH insulin: 27%	p<0.05
	severe Hypoglycaemia	1	glargine: 2.5% NPH insulin: 2.3%	p=NS
Warren 2004	symptomatic hypoglycaemia	2	glargine: 7.3% NPH insulin: 19.1% numbers only for one trial	p<0.05 for both
	nocturnal hypoglycaemia	1	no numbers reported in trial	significantly fewer in glargine group, p=0.0001
	severe hypoglycaemia	0	not reported by studies	

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
glycaemic excursions				
Wang 2003		1	change in FPG levels significantly greater both before and after dinner with insulin glargine (p=0.035, no details); FPG levels at 3:00 am similar between groups (glargine: 133 SE3.6 mg/dL; NPH: 131.4 SE3.6 mg/dL)	
total daily dose				
Warren 2004	insulin use	1	glargine: 23 U/day NPH insulin: 21 U/day	unclear
weight change				
Wang 2003		2	glargine: no change to +2.57 kg NPH insulin: no change to +2.34 kg	p=NS for both studies
complication rates	not reported			
adverse events				
Wang 2003	injection site pain	1	greater number of patients reported injection site pain with insulin glargine compared with NPH insulin (pain usually mild and did not result in discontinuation of treatment)	
Warren 2004	insulin antibodies	1	no increases in either comparison group	
HR quality of life				
Wang 2003	Diabetes Treatment Satisfaction Well-Being Questionnaire	1	no numeric data reported; increases in treatment satisfaction significantly greater for insulin glargine compared to NPH insulin at week 36 (p=0.033); small increase in the perceived frequency of hypoglycaemia in both groups, but no significant difference between groups	
fasting plasma glucose (where HbA1c not reported)				
Duckworth 2007	FPG	1	not reported for groups separately,	similar between groups

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
			decrease from baseline -3.10 to -3.49 mmol/L	
Wang 2003	FPG	1	glargine with 30 µg/mL zinc: -2.8 mmol/L glargine with 80 µg/mL zinc: -2.6 mmol/L NPH insulin: -2.3 mmol/L	p-value not reported
all studies – detemir versus NPH insulin				
HbA1c				
Horvath 2007	HbA1c (%)	2	meta-analysis using different ways of estimating missing SDs weighted mean difference 0.12% (95% CI: 0.01, 0.23) weighted mean difference with pooled SD 0.15% (95% CI: -0.02, 0.32)	first calculation yields significant result (p=0.03) in favour of NPH, but well within pre-defined non-inferiority margin of 0.4% HbA1c; second calculation p=NS
Tran 2007	HbA1c (%)	2	meta-analysis weighted mean difference 0.11% (95% CI: -0.03, 0.26)	p=NS; no significant difference for analysis by different co-interventions
hypoglycaemia				
Horvath 2007	severe hypoglycaemia	2	meta-analysis Peto odds ratio 0.5 (95% CI: 0.18, 1.38)	p=NS
	symptomatic hypoglycaemia	1	detemir: 4.9 events/patient/year NPH insulin: 9.7 events/patient/year relative risk 0.56 (95% CI: 0.42, 0.74)	p<0.001
	overall hypoglycaemia	2	meta-analysis relative risk 0.82 (95% CI: 0.74, 0.90)	p<0.0001
	nocturnal hypoglycaemia	2	meta-analysis relative risk 0.63 (95% CI: 0.52, 0.76)	p<0.00001
Tran 2007	overall hypoglycaemia	1	relative risk 0.91 (95% CI: 0.75, 1.11)	p=NS
	nocturnal hypoglycaemia	1	relative risk 0.66 (95% CI: 0.45, 0.96)	p<0.05
glycaemic excursions				
Tran 2007	8-point blood glucose profiles	2		glucose profiles similar for detemir versus NPH; no difference depending on co-

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
				intervention (insulin aspart or oral anti-hyperglycaemic agents)
total daily dose	not reported			
weight change				
Horvath 2007	weight change	2	difference in weight gain between detemir and NPH -0.8 to -1.6 kg	p<0.05
complication rates				
Horvath 2007	mortality	1	small numbers, no study adequately powered to assess this parameter	
	cardiovascular morbidity	1	very small numbers, no conclusions can be drawn	
	diabetic late complications	1	very small numbers, no conclusions can be drawn	
Tran 2007	mortality	1		none of reported deaths thought to be related to study medication
adverse events				
Horvath 2007	adverse events	2	no difference in frequency of adverse events	
Tran 2007	adverse events	1		no significant differences in adverse events between detemir and NPH
HR quality of life	not reported			

Table 17: Reviews of long acting insulin analogues – subgroup/sensitivity analyses

Study	Outcome (specific time point?)	Factor	n (studies)	Results (of meta-analysis (95% CI) or narrative)	Statistical significance
all studies – glargine versus NPH insulin					
HbA1c					
Horvath 2007	HbA1c (%)	morning glargine versus evening glargine or NPH	1	greater reduction in HbA1c from baseline in the morning group than in evening groups	p<0.05
	HbA1c (%)	insulin-naïve patients	1	no significant difference	p=NS
	HbA1c (%)	patients applying insulin only once daily	1	no significant difference	p=NS
hypoglycaemia					
Horvath 2007	at least one episode of symptomatic hypoglycaemia	insulin-naïve patients	1	glargine: 33% NPH insulin: 43%	p=0.04
	at least one episode of symptomatic hypoglycaemia	patients applying insulin only once daily	1	glargine: 17% NPH insulin: 31%	p<0.002 (wrong numbers in Horvath 2007)
	nocturnal hypoglycaemia	insulin-naïve patients	1	glargine: 10% NPH insulin: 24%	p=0.0001
	nocturnal hypoglycaemia	patients applying insulin only once daily	1	glargine: 15% NPH insulin: 27%	p=NS
complication rates					
Horvath 2007	development of clinically significant macular oedema	patients without insulin pre-treatment versus patients with insulin pre-treatment	1	without insulin pre-treatment glargine: 14% NPH insulin: 4% with insulin pre-treatment glargine: 1.9% NPH insulin: 12.7%	p-value not reported
insulin-naïve, oral antihyperglycaemics – glargine versus NPH insulin					
Duckworth 2007	HbA1c	BMI >28 kg/m2	1	change from baseline glargine: -0.42% NPH insulin: -0.11%	p=0.0237
Wang 2003	nocturnal hypoglycaemia	patients reaching / not	1	52 weeks	p<0.05 for both

Study	Outcome (specific time point?)	Factor	n (studies)	Results (of meta-analysis (95% CI) or narrative)	Statistical significance
		reaching FPG target (≤120 mg/dL)		target reached glargine: 12.6% NPH insulin: 28.8% target not reached glargine: 9.0% NPH insulin: 21.4%	subgroups glargine versus NPH

4.3.7 Glycaemic control

Trials generally showed a reduction in HbA1c from baseline to end of study, but without any difference between comparison groups. Horvath and colleagues carried out two meta-analyses regarding HbA1c results for insulin glargine versus NPH insulin, one including only for the four for which standard deviations were available or could be calculated, and the other including studies where this was not the case and where a pooled standard deviation was used (two extra studies, i.e. six in the meta-analysis). In both analyses, there was no significant difference between glargine and NPH in end of study HbA1c, with a weighted mean difference (WMD) between groups of around 0 (for all six studies WMD 0.0 (95% CI: -0.01, 0.1)). Similarly, Tran and colleagues in their meta-analysis of seven studies found no significant difference in HbA1c values between glargine and NPH (WMD 0.05 (95% CI: -0.07, 0.16). For the remaining reviews, results were presented according to whether patients had had previous insulin treatment without oral treatment or were previously insulin-naïve with concomitant oral treatment. For the two trials (or rather one with subgroup analysis) of people with previous insulin treatment, HbA1c at the end of study was similar between the glargine and NPH groups (reduction from baseline between -0.35 and -0.6%). For the trials in insulin-naïve patients using concomitant oral therapy, most trials showed no significant difference between glargine and NPH at the end of the study either, except in the study by Fritsche 2003, where after 24 weeks of treatment, HbA1c was significantly more reduced with morning glargine than with evening glargine or evening NPH (-1.24% versus -0.96% and -0.84% respectively). Subgroup analyses in two trials, one of insulin-naïve patients and one of patients applying insulin once rather than twice daily also showed no difference in HbA1c values between groups. However, one study found a significant effect for HbA1c in favour of glargine in a subgroup analysis of patients with a BMI of more than 28 kg/m2 (HbA1c change from baseline -0.42% with glargine and -0.11% with NPH, p=0.024). There was no significant difference in end of study HbA1c values in the two studies of insulin detemir versus NPH, irrespective of previous treatment and co-interventions.

Where reported, the percentages of patients reaching the fasting plasma glucose or HbA1c targets were also similar between insulin glargine and NPH insulin, except in the study by Fritsche 2003, where significantly more patients reached the target with morning glargine than with evening glargine or evening NPH.

4.3.8 Hypoglycaemia

Severe hypoglycaemia. In their meta-analysis of studies of glargine versus NPH, Horvath and colleagues summarised four studies of six months' duration (to avoid imbalance due to different study durations) and found no significant difference in the frequency of severe hypoglycaemia between glargine and NPH (Peto odds ratio 0.70 (95% CI: 0.40, 1.23). There was no significant difference – or no statistical information available – for the remaining three studies assessing severe hypoglycaemia that were not included in the meta-analysis. Similarly, Tran and colleagues did a meta-analysis of severe hypoglycaemia in four studies and found no significant difference between glargine and NPH (relative risk 1.09 (95% CI: 0.56, 2.12) and no significant difference when analysing trials depending on their co-interventions. In the remaining reviews, no significant differences in severe hypoglycaemia were reported for patients on previous insulin therapy or for previously insulin-naïve patients on oral anti-hyperglycaemic therapy (and continuing oral therapy). Similarly, no significant difference was found for severe hypoglycaemia for the two trials of insulin detemir versus NPH insulin.

Overall and symptomatic hypoglycaemia. Definition of "overall" and "symptomatic" hypoglycaemia varied, with some reviews summarising under "overall" hypoglycaemia "overall symptomatic hypoglycaemia" and some referring to "any hypoglycaemic even". Results for this outcome were inconclusive. In their meta-analysis of three six-month studies of glargine versus NPH, Horvath and colleagues found significantly fewer symptomatic

hypoglycaemic episodes with glargine than with NPH (relative risk 0.84 (95% CI: 0.75, 0.95), but only one of the remaining four studies reporting this outcome found a significant effect in favour of glargine. Similarly, the one study reporting overall hypoglycaemia found no significant difference between glargine (morning or evening) and NPH.

Tran and colleagues included six trials in their meta-analysis of overall hypoglycaemia and found a significant difference in favour of glargine (relative risk 0.89 (95% CI: 0.83, 0.96). Considering studies in patients previously on insulin separately, the trial by Rosenstock 2001[159] found no significant effect on overall symptomatic hypoglycaemia in favour of glargine, whereas the subgroup analysis of that study including patients on once daily insulin did (46.2% versus 60.4% of patients with one or more episodes). In the analyses of insulin-naïve patients on oral therapy, Duckworth and colleagues summarised data for overall symptomatic hypoglycaemia in six studies and found a significant effect in favour of glargine versus NPH in four of these (where between 10 and 13% fewer patients had symptomatic hypoglycaemias in the glargine groups, or between 2.5 and 3.8 fewer events occurred per patient-year). Warren and colleagues and Wang and colleagues included two studies in their analyses and found significant differences in favour of glargine for both of them for hypoglycaemic episodes / symptomatic hypoglycaemia (10 or more percent less with glargine). For insulin detemir, Horvath and colleagues found a significant difference in favour of detemir in one study for symptomatic hypoglycaemia (not reported by the other study) (4.9 versus 9.7 events per patient-year), and for overall hypoglycaemia the meta-analysis of the two included studies gave a significant result (relative risk 0.82 (95% CI: 0.74, 0.90, p<0.0001)).

Nocturnal hypoglycaemia. Results for nocturnal hypoglycaemias were clearly in favour of the long-acting insulin analogues. In their meta-analysis of three six-month studies of glargine versus NPH, Horvath and colleagues obtained a relative risk of 0.66 (95% CI: 0.55, 0.80, p<0.0001). The three studies not included in the meta-analysis but reporting on nocturnal hypoglycaemia also all found a significant result in favour of glargine. Tran and colleagues included five studies in their meta-analysis and obtained a relative risk for nocturnal hypoglycaemias of 0.57 (95% CI: 0.44, 0.74) in favour of glargine. Considering studies in patients previously on insulin separately, the trial by Rosenstock 2001 found a significant effect on nocturnal hypoglycaemia (31.3 versus 40.2% with at least one episode of nocturnal hypoglycaemia, p=0.016), whereas the subgroup analysis of that study including patients on once daily insulin did not. All trials of previously insulin-naïve patients on oral therapy found significantly fewer nocturnal hypoglycaemias with insulin glargine than with NPH insulin (between ~10 to 20% fewer patients with nocturnal hypoglycaemias with glargine). One trial also reported that significantly more patients using glargine reached the HbA1c target of 7% or less without nocturnal hypoglycaemias (33% versus 27% using NPH, p<0.05). With respect to insulin detemir, the meta-analysis of nocturnal hypoglycaemia in the two trials by Horvath and colleagues obtained a relative risk of 0.63 (95% CI: 0.52, 0.76, p<0.00001) in favour of detemir (similar relative risk in the review by Tran and colleagues , which only reported data from one trial).

4.3.9 Glycaemic excursions

Data on glycaemic excursions were only systematically summarised by the review by Tran and colleagues who reported data from three studies that had measured eight point glucose profiles. There was generally no statistically significant difference between glucose profiles for glargine versus NPH with the exception of two trials. One study showed significantly lower pre-dinner glucose levels for glargine, and the other reported significant values for morning (but not evening) glargine in comparison to evening NPH. For insulin detemir, eight point glucose profiles were similar in comparison to NPH, irrespective of the co-intervention.

4.3.10 Total daily insulin dose

Total daily insulin dose was not systematically reported by the systematic reviews. Warren and colleagues reported for one trial of patients with previous insulin use, that patients on pre-trial once-daily NPH used slightly more insulin at trial end than at baseline, and patients on more than once-daily NPH pre-trial used slightly less insulin in the glargine group at the end of the trial (reduced by 4.4 U/day) than patients treated with NPH who used about the same (no more data presented). For one trial of previously insulin-naïve patients on oral therapy Warren and colleagues reported similar insulin consumption of 23 U/day for glargine and 21 U/day for NPH, but statistical information was not provided. Insulin daily doses were not provided for the trials using insulin detemir.

4.3.11 Weight change

Weight change was not systematically reported by the systematic reviews. Wang and colleagues reported a significant change in weight gain for a trial of patients previously treated with insulin, with patients receiving insulin glargine gaining significantly less weight than patients on NPH insulin (+0.4 kg versus +1.4 kg, $p<0.001$). In two other trials of previously insulin-naïve patients on oral therapy, no significant difference in weight change was seen between the glargine and NPH insulin groups (total changes between no change and +2.6 kg). Horvath and colleagues reported significantly less weight gain with insulin detemir than NPH insulin with a weight difference of between 0.8 and 1.6 kg between the comparison groups ($p<0.05$).

4.3.12 Diabetic complications

Data on diabetic complications were not systematically reported by the reviews – and were generally not available in the trials (and trials were underpowered for assessing such outcome parameters). Several reviews – and trials – reported mortality data, but numbers were generally small and deaths were considered to be unrelated to the trial interventions. No data on diabetic late complications were included in any of the reviews, but Horvath and colleagues found some information on diabetic retinopathy for one trial of patients with previous insulin treatment and for one trial of patients on oral therapy (some of whom had been insulin pre-treated). In the trial including oral therapy, 8.4% of patients in the insulin glargine group and 14% of patients in the NPH insulin group who had had no retinopathy at baseline developed non-proliferative retinopathy, and 1.8 and 2.4% respectively developed clinically significant macular oedema. Progression of retinopathy by more than three stages was seen in 5.9% of patients on glargine and 9.1% of patients on NPH (no significance values reported). In the study of patients on previous insulin-treatment without oral therapy, significantly more patients on glargine had a progression of retinopathy by three or more stages than with NPH (7.5 versus 2.7%, $p=0.028$). In the study of patients on concomitant oral therapy, no significant difference in development of clinically significant macular oedema was seen between glargine and NPH (11.2% with glargine, 6.5% with NPH, p=NS). However, there was a marked difference in this outcome between previously insulin-naïve patients and patients pre-treated with insulin. In insulin –naïve patients , the development of clinically significant macular oedema in 14% in the glargine group and 4% in the NPH group. In contrast, patients previously treated with insulin had incidences of 1.9% and 12.7% (no significance reported). Numbers of diabetic late complications occurring in one of the trials of insulin detemir were too small to draw any conclusions.

4.3.13 Adverse events

No significant differences in adverse events, number of patients with adverse events, severe adverse events, or withdrawals because of adverse events were generally seen between insulin glargine or detemir and NPH insulin. There was some indication in some trials that a greater number of patients on insulin glargine reported injection site pain than patients on

NPH insulin, but pain was usually mild and did not result in discontinuation of treatment. Where reported, no differences in insulin anti-bodies were seen between study groups. None of the studies were long enough to assess any longer term effects.

4.3.14 Health-related quality of life

No data were reported on health-related quality of life. Wang and colleagues and Horvath and colleagues reported on one study each that suggested that there was a significantly greater improvement of treatment satisfaction with insulin glargine than with NPH insulin.

4.3.15 Additional reviews identified after completion of this review

Two systematic reviews, both including meta-analyses, were identified after completion of the main analyses for this review. The review by Bazzano and colleagues (2008)[145] focussed on the safety and efficacy of glargine compared with NPH insulin in type 2 diabetes, whereas the review by Monami and colleagues (2008)[146] considered both glargine and detemir compared with NPH insulin in type 2 diabetes. Bazzano and colleagues included 12 RCTs and Monami and colleagues included 11 RCTs of glargine versus NPH insulin and three RCTs of detemir versus NPH insulin. All of the RCTs included in the two reviews have been considered by the present review.

The review by Bazzano and colleagues was of good quality. The search strategy was thorough, inclusion criteria were described, as was data extraction, quality assessment, and data analysis. Study flow was shown. Descriptive and quality data were given for each included RCT. The review by Monami and colleagues was also of good quality. Inclusion criteria, search strategies, data extraction, quality assessment, and data analysis were described. Study flow was shown and descriptive and quality data were shown for each trial.

Both reviews suggested that there was no significant difference between glargine or detemir and NPH insulin for glycaemic control. Bazzano and colleagues reported slightly less patient-reported hypoglycaemia with glargine than with NPH insulin, and Monami and colleagues reported less symptomatic and nocturnal hypoglycaemia with glargine or detemir versus NPH. Bazzano and colleagues reported slightly less weight gain with NPH than with glargine, whereas Monami and colleagues reported no differences in BMI when comparing glargine and NPH, but a lower BMI with detemir than with NPH insulin.

4.3.16 Review conclusions and research recommendations

Review conclusions and recommendations are shown in Table 18.

Table 18: Conclusion and recommendations – reviews of long acting insulin analogues

Study	Conclusions (medical effectiveness)	Recommendations for research	Comments
Bazzano 2008 [145]	HbA1c: results indicate that there is no difference in glycaemic control between glargine and NPH insulin hypoglycaemia: results indicate that there is less patient-reported hypoglycaemia with glargine than NPH in patients with type 2 diabetes (absolute differences small but significant for all types, symptomatic and nocturnal hypoglycaemia; not significant for rates of hypoglycaemia) glycaemic excursions: no relevant trial data reported total daily dose: no significant difference between groups weight change: patients on NPH insulin gained slightly less weight than patients on glargine complication rates: no relevant trial data reported adverse events: no relevant trial data reported health-related quality of life: no relevant trial data reported		review financially supported by Eli Lilly and Company
Duckworth 2007 [140]	HbA1c: review suggests that insulin glargine and NPH insulin are similarly effective with respect to achieving and maintaining glucose control hypoglycaemia: insulin glargine is associated with a significantly lower risk of hypoglycaemia, particularly nocturnal hypoglycaemia, compared to NPH insulin glycaemic excursions: no relevant trial data reported total daily dose: no relevant trial data reported weight change: no relevant trial data reported complication rates: no relevant trial data reported adverse events: no relevant trial data reported health-related quality of life: no relevant trial data reported	none explicit; suggested that quality of life research would be useful in eliciting which insulin patients prefer	
Horvath 2007 [141]	HbA1c: no significant difference between insulin glargine or insulin detemir and NPH insulin (statistically significant but clinically unimportant superiority for detemir versus NPH) hypoglycaemia: no significant difference for severe hypoglycaemia; rate of overall, symptomatic and nocturnal hypoglycaemia significantly lower with glargine or detemir than with NPH; but authors suggest that there is only a minor clinical effect	long term follow-up data needed to assess effectiveness in terms of diabetes late complications and safety issues studies in young and old	

Study	Conclusions (medical effectiveness)	Recommendations for research	Comments
	glycaemic excursions: no relevant trial data reported total daily dose: no relevant trial data reported weight change: no conclusions given complication rates: only limited information available adverse events: no significant difference between glargine or detemir and NPH insulin health-related quality of life: no relevant trial data reported; limited data suggesting more treatment satisfaction with glargine than NPH insulin (but only one study and data potentially unreliable)	patients (i.e. younger and older than the age range of 55-62 years in the included studies) more uniform and rigorous reporting of results; including definitions of different types of hypoglycaemia	
Monami 2008 [174]	HbA1c: the use of long-acting insulin analogues in type 2 diabetes patients does not seem to provide a better glycaemic control in comparison with NPH insulin hypoglycaemia: treatment with long-acting insulin analogues in comparison with NPH reduces the risk of nocturnal and symptomatic hypoglycaemia glycaemic excursions: no relevant trial data reported total daily dose: no relevant trial data reported weight change: detemir, but not glargine, could be associated with smaller weight gain than NPH insulin complication rates: no relevant trial data reported adverse events: no relevant trial data reported health-related quality of life: no relevant trial data reported	longer term data are needed to assess the clinical relevance of differences in the effects on weight gain of glargine / detemir	
Tran 2007 [142]	HbA1c: no significant difference in HbA1c levels with insulin glargine or detemir in comparison to NPH hypoglycaemia: risk of nocturnal hypoglycaemia significantly reduced with insulin glargine compared to NPH, probably also with insulin detemir glycaemic excursions: no evidence for significant difference in eight point blood glucose profiles when comparing insulin glargine or detemir with NPH total daily dose: no relevant trial data reported weight change: some trials reported increases in weight, but no differences between comparison groups were quoted complication rates: no deaths in trials related to study medication adverse events: no significant differences between comparison groups	None	6 trials in patients with type 2 diabetes were identified after the completion of the assessment; the authors conclude that the results of those trials were unlikely to change the conclusions of the review; only 3 of the extra trials are valid comparisons of long-acting insulin analogues with NPH and 2 are included in the review by Horvath 2007, the third is presented below

Study	Conclusions (medical effectiveness)	Recommendations for research	Comments
	reported health-related quality of life: no relevant information identified		
Wang 2003 [143]	HbA1c: insulin glargine appears to have equal clinical efficacy as NPH insulin hypoglycaemia: insulin glargine is associated with significant reductions in nocturnal hypoglycaemia compared to NPH insulin glycaemic excursions: insulin glargine is associated with lower FPG and FBG levels compared to NPH insulin total daily dose: no relevant trial data reported weight change: no conclusions given complication rates: no relevant trial data reported adverse events: insulin glargine was associated with greater pain at the injection site than NPH insulin health-related quality of life: greater treatment satisfaction has been reported with insulin glargine than with NPH insulin	none (only indirect see Comments)	the authors comment that the place of insulin glargine in routine clinical practice remains to be determined; studies were limited by their open-label design, inadequate sample sizes, use of individual dose titration to achieve FPG ≤120 mg/dL, lack of information on co-interventions; use should be limited in patients with type 2 diabetes to those taking multiple daily injections of basal/bolus regimens who have not achieved optimal glycaemic control with NPH insulin who have episodes of symptomatic hypoglycaemia; in insulin-naïve patients taking oral anti-diabetic agents, use of insulin glargine should be limited to those who continue to have elevated morning blood glucose levels and episodes of nocturnal hypoglycaemia while taking a combination of oral agents or a combination of bedtime NPH insulin with oral antidiabetic agents
Warren 2004 [144]	HbA1c: insulin glargine does not appear to improve long term glycaemic control compared to NPH insulin hypoglycaemia: insulin glargine is effective in reducing the number of nocturnal hypoglycaemic episodes, especially when compared to once daily NPH; equivocal evidence regarding control of symptomatic hypoglycaemia; no evidence of improvement on severe hypoglycaemia	studies of quality of life required focussing on assessing both the short term immediate impact of acute episodes of hypoglycaemia and the longer term impact of	clinical relevance unclear, as trial patients may have used different regimens than patients in usual clinical practice

Study	Conclusions (medical effectiveness)	Recommendations for research	Comments
	glycaemic excursions: no relevant trial data reported total daily dose: there are insufficient data to make reliable conclusions regarding insulin dose weight change: no conclusions given complication rates: no relevant trial data reported adverse events: most common adverse event was injection site pain; where reported, no significant increases in insulin antibodies in either comparison group health-related quality of life: no relevant trial data reported	living with a reduced fear of hypoglycaemia	

Although there were some differences in assessment of the data between reviews, all reviews essentially came to the same conclusions. All reviews concluded that insulin glargine – and insulin detemir where assessed – led to a glycaemic control equivalent to that using NPH insulin.

Regarding the occurrence of hypoglycaemia, all reviews concluded that insulin glargine – and where assessed, probably also insulin detemir – were more effective at reducing nocturnal hypoglycaemias than NPH insulin. In addition, there was no between group differences for severe hypoglycaemias, and the evidence was inconclusive regarding overall / symptomatic hypoglycaemias (with some reviews being more optimistic than others). However, the review by Horvath and colleagues suggested that even the effect on nocturnal hypoglycaemias was only minor. Only Tran and colleagues systematically assessed glycaemic excursions and concluded that overall, there was no significant difference in glucose profiles between glargine or detemir and NPH insulin. None of the studies came to any firm conclusions regarding total insulin dose or weight change. Not enough trial information was available to make any conclusions about diabetic secondary complications or health-related quality of life. Overall, reviews concluded that there were no significant differences in adverse events between glargine or detemir than with NPH insulin (although there may be slightly more injection site pain with glargine, as reported by some reviews).

In some of the reviews, it was suggested that the clinical relevance of the findings was unclear: trials were thought to have major design flaws (e.g. all being open-label, giving limited information on important factors such as co-interventions etc.). In addition, Warren and colleagues suggested that trial patients may have used different regimens than patients in usual clinical practice.

Not all of the reviews included clear recommendations for research; where given, research recommendations included:

- Need for long term follow-up data to assess effectiveness in terms of diabetes late complications and safety issues
- Need for studies in young and old patients (i.e. younger and older than the age range of 55-62 years in the included studies)
- Need for more uniform and rigorous study design and reporting of results; including definitions of different types of hypoglycaemia
- Need for studies of quality of life focussing on assessing both the short term immediate impact of acute episodes of hypoglycaemia and the longer term impact of living with a reduced fear of hypoglycaemia; and other aspects of the impact of the different insulin on patients' quality of life

4.4 Randomised Controlled Trials

4.4.1 Search results

Fourteen papers were identified as potentially relevant RCTs. Of these, six fulfilled the inclusion criteria, but one[175] turned out to refer to a trial Hermansen, 2006 143 /id} already included in the review by Horvath and colleagues (2007). One abstract and one full publication referred to the same trial [176,177] of insulin glargine versus insulin detemir. Full data extraction was done for five trials.[143,177-180] Table 19. shows the excluded trials. Trials were excluded because they did not include the comparisons of interest (e.g. no comparison with another basal insulin), because data were inadequate or because no outcomes of interest were investigated.

Table 19: Table of excluded trials – long acting insulin analogues

Study	Reason for exclusion
Holman 2007 [181]	not compared with other basal
Hermansen 2007 [182]	not compared with other basal
Klein 2006 [183]	very short duration and no outcomes of interest
Kolendorf 2005 [184]	inadequate data
Rosenstock 2006 [170]	not one of the comparisons specified in protocol

4.4.2 Description of trials

Characteristics of the included trials are shown in Appendix 5

Design. All five trials were parallel, open-label randomised controlled trials sponsored by industry (where reported). Trial duration was between 12 and 52 weeks. The LEAD trial by Pan and colleagues (2007)[179] was carried out in China, Korea and France, the trial by Wang and colleagues (2007)[185] was carried out in China, the PREDICTIVE-BMI trial reported by Montanana and colleagues (2007)[178] was carried out in Spain, and the trials by Philis-Tsimikas and colleagues (2006)[180] and Rosenstock and colleagues(2008)[177] were carried out in various European countries and the USA.

Participants. The trials included between 24 and 582 participants, with between 8 and 291 in each comparison group. The total number of participants was 1818. The LEAD trial was done in Asian participants only, and the trial by Wang and colleagues in Chinese participants. The LEAD trial, and the trials by Philis-Tsimikas 2006, Wang 2007, and Rosenstock 2008 were done in insulin-naïve patients with concomitant oral anti-hyperglycaemia agents, while the PREDICTIVE-BMI trial was done in participants who had been on insulin (two daily doses, at least one premix) for three months or more. The LEAD trial did not detail any required specific previous oral therapy, while the trial by Wang 2007 required previous treatment with sulphonylurea or combination treatment. The trial by Philis-Tsimikas 2006 specified that previous oral therapy had to have been with metformin, an insulin secretagogue or a combination of the two; at US centres, concomitant treatment with thiazolidinediones (TZD) was permitted throughout the study period, whereas at European centres TZD was to be discontinued before initiation of insulin treatment; use of an alpha-glucosidase inhibitor was permitted but only in combination with another oral agent. The trial by Rosenstock 2008 required previous treatment with one or two oral agents (metformin, insulin secretagogues, alpha-glucosidase inhibitors). The PREDICTIVE-BMI trial included patients who were already overweight (BMI between 25 and 40 kg/m2). Further details of inclusion and exclusion criteria of the trials can be found in **Error! Reference source not ound.**. Trial participants had a mean age of between 56 and 62 years. Between 41 and 62% of women took part in the trials. Ethnicity was reported for the Asians in the LEAD trial, who came from 10 different countries of origin (the largest groups from China and South Korea); 99% of participants in the PREDICTIVE-BMI trial were white, and between 86 and 90% of participants in the trial by Rosenstock 2008 were white. Mean diabetes duration was between nine and 16 years. Details of previous diabetes medication for the two trials are shown in **Error! Reference source not found.**. Baseline BMI was between 25 kg/m2 and 32 g/m2.

Interventions. The trial by Philis-Tsimikas 2006 compared three intervention groups, while the other trials compared two groups. In the LEAD trial, insulin glargine once daily at bedtime plus once daily glimepiride (3 mg) in the morning was compared with NPH insulin at bedtime plus 3 mg glimepiride once daily in the morning. In both arms, insulin was titrated to a target FBG ≤6.7 mmol/L, starting at insulin dose of 0.15 U/kg/day. The trial included a screening phase of three to four weeks in which oral treatments were standardised to 3 mg glimepiride and patients were given training in self-administration of insulin and self-monitoring of blood glucose levels.

Wang 2007 compared insulin glargine plus extended-release glipizide with NPH insulin plus plus extended-release glipizide. Glargine or NPH were injected at bedtime with an initial dose of 0.15 IU/kg/day and then titrated to reach a fasting blood glucose value of <6.7 mmol/L. Glipizide was given before breakfast (5 mg/day). During a two-week screening phase, previous oral medication was stopped and patients were initiated on 5 mg/day extended-release glipizide. They also received diabetes education.

In the PREDICTIVE-BMI trial, once daily evening insulin detemir was compared with once daily evening NPH insulin. In both groups, basal insulin was continually and individually titrated, aiming for pre-breakfast plasma glucose levels of ≤6.1 mmol/L without levels of hypoglycaemia considered unacceptable to the patient. In addition, all patients received insulin aspart at the main meals (individually titrated aiming for postprandial glucose levels of ≤10.0 mmol/L); concomitant treatment with metformin was also allowed (used by ~50% of patients on detemir and ~58% of patients on NPH).

In the trial by Philis-Tsimikas 2006, insulin detemir once daily before breakfast was compared with insulin detemir once daily in the evening as well as to human NPH insulin once daily in the evening. The initial dose of treatment was 10 IU (U), doses were titrated at clinic visits or by telephone at least once every four weeks based on the mean of three plasma glucose levels measured on three consecutive days; in patients receiving detemir in the morning, the dose was titrated to aim for pre-dinner plasma glucose concentration of ≤6.0 mmol/L; in patients receiving detemir or NPH in the evening, titration was aimed to achieve pre-breakfast plasma glucose concentration of ≤6.0 mmol/L. Oral anti-hyperglycaemic therapy and dose was to remain unchanged.

In the trial by Rosenstock 2008, detemir was compared with glargine. The detemir group received an injection once daily in the evening or twice daily (morning and evening). Glargine was injected once daily in the evening. In both groups, basal insulin was initiated at once daily (evening) 12 U and titrated according to a structured treatment algorithm; people on detemir were allowed to receive an additional morning dose i.e. pre-dinner plasma glucose was >7.0 mmol/L, but only if pre-breakfast PG was <7.0 mmol/L or nocturnal hypoglycaemia (major episode or PG ≤4.0 mmol/L) precluded the achievement of the fasting plasma glucose target. Insulin was injected using a pen-injector. The fasting plasma glucose was ≤6.0 mmol/L in the absence of hypoglycaemia. Oral glucose-lowering therapy, diet and physical activity recommended to remain stable during the study; no meal-time insulin was allowed.

Outcomes. In the LEAD trial, the trial by Philis-Tsimikas 2006, and the trial by Rosenstock 2008 the primary outcome measure was HbA1c. No primary outcome measure was specified the trial by Wang 2007. The primary outcome in the PREDICTIVE-BMI trial was weight change. All trials reported outcomes related to HbA1c, hypoglycaemia, and weight change. Blood glucose profiles, total daily insulin dose, and adverse events were also reported by most of the trials. None of the trials reported health-related quality of life or diabetic secondary complications.

4.4.3 Trial quality

Details of the quality assessment of the trials are shown in Table 20.

Table 20: Quality of included trials – long acting insulin analogues

	Pan 2007	Wang 2007	Montanana 2008	Philis-Tsimikas 2006	Rosenstock 2008
appropriate and clearly focused question	yes	yes	yes	yes	yes
method of randomisation	not described	not described	described, adequate	described, adequate	described, adequate
allocation concealed	not reported	not reported	yes	unclear	yes
participants blinded	no	not reported	no	no	no
outcome assessors blinded	no	not reported	not reported	no	unclear
all relevant outcomes measured in standard, valid, reliable way	yes	yes	yes	yes	yes
proportion of participants excluded / lost to follow-up	4 patients withdrew consent after randomisation and received no study medication; 1 received medication but provided no outcome measures; 49 were excluded for major protocol violations; no further details	not reported (no drop-outs/withdrawals?)	7 withdrawals in detemir group, 12 withdrawals in NPH group, reasons listed, no significant difference between groups	18, 16 and 17 in morning detemir, evening detemir and evening NPH groups, reasons listed, no significant difference between groups	60 withdrawn in detemir group (23 adverse events, 3 ineffective therapy, 10 non-compliant, 24 other reasons); 39 withdrawn in glargine group (11 adverse events, 2 ineffective therapy, 15 non-compliant, 11 other reasons)
handling of missing data	not reported	not reported	last observation carried forward	last observation carried forward	last observation carried forward
intention-to-treat analysis performed	yes	not reported	yes	yes	yes
statistical analysis appropriate	yes	yes	yes	yes, non-inferiority analysis	yes, non-inferiority analysis
only difference between groups is treatment under investigation	yes	yes	yes	yes	yes; although detemir was dosed twice daily in some patients
results in multi-centre studies comparable for all sites	not reported	not applicable	not reported	not reported	unclear

	Pan 2007	Wang 2007	Montanana 2008	Philis-Tsimikas 2006	Rosenstock 2008
groups comparable at baseline	yes	yes	yes	yes	yes
SUMMARY					
How well was study done to minimise bias: (++ / + / -)	(-)	(-)	(+)	(+)	(+)
What is the likely direction in which bias might affect study results?	positive effects of study drug exaggerated	positive effects of study drug exaggerated			
Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	probably	probably	yes	yes	yes
Are the results of this study directly applicable to the patient group targeted by this guideline?	no (Asian patients only)	no (Chinese study)	yes	yes	yes

The LEAD trial and the trial by Wang 2007 had a number of quality deficits, while the trials by Philis-Tsimikas 2006 and Rosenstock 2008 and the PREDICTIVE-BMI trial were of better quality.

In the LEAD trial, the method of randomisation was not described, nor was allocation concealment. Participants and outcome assessors were not blinded. As far as reported, all relevant outcomes were measured in a standard, valid, reliable way. The proportion of participants excluded / lost to follow-up was only reported for the whole study group, but not for comparison groups separately, with five patients (1%) withdrawing before receiving treatment or not providing any outcomes, and 49 excluded due to major protocol violations (11%). Intention-to-treat analysis was performed, but handling of missing data was not reported. The comparison groups were comparable at baseline. The study population was 100% Asian.

The trial by Wang 2007 was underpowered (only 24 participants), randomisation and allocation concealment were not described, neither was blinding. As far as reported, all relevant outcomes were measured in a standard, valid, reliable way. Withdrawals or drop-outs were not mentioned, handing of missing data and intention-to-treat analysis were not reported. The study groups were comparable at baseline.

The PREDICTIVE-BMI trial had adequate randomisation and allocation concealment. Participants were not blinded, blinding of outcome assessors was not reported. As far as reported, all relevant outcomes were measured in a standard, valid, reliable way. The proportion of participants excluded / lost to follow-up was reported with reasons for each comparison group separately, with no significant differences between study groups (7% withdrawals / losses to follow-up). Intention-to-treat analysis was performed, and handling of missing data was by last observation carried forward. The comparison groups were comparable at baseline.

In the trial by Philis-Tsimikas 2006, the method of randomisation was described and adequate, but allocation concealment was uncertain. Participants and outcome assessors were not blinded. As far as reported, all relevant outcomes were measured in a standard, valid, reliable way. The proportion of participants excluded / lost to follow-up was reported with reasons for each comparison group separately, with no significant differences between study groups (11% withdrawals / losses to follow-up). Intention-to-treat analysis was performed, and handling of missing data was by last observation carried forward. The comparison groups were comparable at baseline.

The trial by Rosenstock 2008 had adequate randomisation and allocation concealment. Participants were not blinded, blinding of outcome assessors was not reported. As far as reported, all relevant outcomes were measured in a standard, valid, reliable way. The proportion of participants excluded / lost to follow-up was reported with reasons for each comparison group separately, with no significant differences between study groups (10% withdrawals / losses to follow-up). Intention-to-treat analysis was performed, and handling of missing data was by last observation carried forward. The data were analysed in a non-inferiority analysis. The comparison groups were comparable at baseline.

4.4.4 Results

Results for the five trials are shown in Table 21.

Table 21: Main results of included trials – long acting insulin analogues

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
insulin-naïve, oral antihyperglycaemics – glargine versus NPH insulin					
HbA1c					
Pan 2007 (LEAD study)	HbA1c (%)	**glargine**: 9.02 SD0.88 % **NPH insulin**: 9.05 SD0.84 %	**glargine**: 8.03% **NPH insulin**: 8.28%	**glargine**: -0.99% **NPH insulin**: -0.77% difference in ITT population 0.22 (95% CI: 0.02, 0.42)	p=NS for per-protocol population, p=0.0319 for ITT population
	patients achieving target HbA1c (<7.5%) (%)		**glargine**: 38.1% **NPH insulin**: 30.3%		p=NS
	patients achieving target HbA1c (<7.5%) without nocturnal hypoglycaemia (%)		**glargine**: 22.9% **NPH insulin**: 14.0%		p=0.017
	patients achieving target FBG (≤120 mg/dL) (%)		**glargine**: 62.3% **NPH insulin**: 58.7%		p=NS
Wang 2007	HbA1c (%)	**glargine**: 8.77 SD1.18 % **NPH insulin**: 8.75 SD1.24 %	**glargine**: 7.62 SD0.98 % **NPH insulin**: 7.43 SD0.73 %		p=NS
hypoglycaemia					
Pan 2007 (LEAD study)	number of hypoglycaemic episodes		**glargine**: 682 **NPH insulin**: 1019		p<0.004
	symptomatic hypoglycaemia		**glargine**: 515 **NPH insulin**: 908		p<0.0003
	severe hypoglycaemia		**glargine**: 5 **NPH insulin**: 28		p<0.03
	nocturnal hypoglycaemic episodes		**glargine**: 221 **NPH insulin**: 620		p<0.001
Wang 2007	all hypoglycaemic events		**glargine**: 2 in 2 patients		p=NS

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
			NPH insulin: 6 in 4 patients		
	nocturnal hypoglycaemic events		**glargine**: 1 in 1 patient **NPH insulin**: 4 in 4 patients		p=0.028
glycaemic excursions					
Pan 2007 (LEAD study)	eight-point blood glucose profiles			eight-point blood glucose profiles similar between groups at study end, except for post-dinner, where BG concentration in glargine group was significantly lower than in NPH group (236 mg/dL versus 249 mg/dL, p=0.044)	p=0.044
Wang 2007 (continuous glucose monitoring system)	average blood glucose		**glargine**: 8.2 SD1.2 mmol/L **NPH insulin**: 8.0 SD2.0 mmol/L		p=NS
	SD of blood glucose		**glargine**: 1.4 SD0.4 mmol/L **NPH insulin**: 2.3 SD0.5 mmol/L		p<0.05
	SD of FPG		**glargine**: 0.7 SD0.4 mmol/L **NPH insulin**: 1.5 SD0.7mmol/L		p<0.05
	SD of bedtime PG		**glargine**: 1.2 SD0.4 mmol/L **NPH insulin**: 2.0 SD0.7mmol/L		p<0.05
	blood glucose – pre-breakfast		**glargine**: 5.5 SD0.8 mmol/L **NPH insulin**: 5.8 SD1.5 mmol/L		p=NS
	blood glucose – 2 h post-breakfast		**glargine**: 9.8 SD2.6 mmol/L **NPH insulin**: 10.4 SD1.9 mmol/L		p=NS

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
	blood glucose – pre-lunch		**glargine**: 5.9 SD1.0 mmol/L **NPH insulin**: 6.6 SD1.2 mmol/L		p=NS
	blood glucose – 2 h post-lunch		**glargine**: 9.8 SD1.5 mmol/L **NPH insulin**: 10.2 SD1.8 mmol/L		p=NS
	blood glucose – pre-supper		**glargine**: 6.0 SD0.7 mmol/L **NPH insulin**: 7.1 SD1.0 mmol/L		p<0.05
	blood glucose – 2 h post-supper		**glargine**: 10.8 SD1.6 mmol/L **NPH insulin**: 11.7 SD1.4 mmol/L		p=NS
	blood glucose – bedtime		**glargine**: 7.8 SD1.2 mmol/L **NPH insulin**: 9.2 SD2.0 mmol/L		p<0.05
	blood glucose – 3:00 am		**glargine**: 5.1 SD0.8 mmol/L **NPH insulin**: 4.2 SD1.4 mmol/L		p<0.05
total daily dose					
Pan 2007 (LEAD study)	daily insulin dose	**glargine**: 9.6 SD1.5 U **NPH insulin**: 9.8 SD1.9 U	**glargine**: 32.1 SD17.6 U **NPH insulin**: 32.8 SD18.9 U		p=NS
Wang 2007	daily insulin dose		**glargine**: 18.5 SD7.5 IU **NPH insulin**: 19.0 SD8.4 IU		p=NS
weight change					
Pan 2007 (LEAD study)	BMI	**glargine**: 24.8 SD3.1 kg/m2 **NPH insulin**: 25.1 SD3.3 kg/m2		**glargine**: +1.40 kg/m2 **NPH insulin**: +1.29 kg/m2	p=NS
Wang 2007	weight			**glargine**: +1.47 SD1.04 kg	p=NS

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
				NPH insulin: +1.20 SD1.17 kg	
complication rates - not reported					
adverse events					
Pan 2007 (LEAD study)	treatment-emergent adverse events that were possibly treatment-related (66 events in 45 patients)		**glargine**: 22 patients **NPH insulin**: 23 patients majority related to injection-site reactions (45 events in 31 patients)		p not reported
	serious adverse events			no significant difference between groups, none of events considered unusual for the demographic group studied	p=NS
HR QoL	not reported				
previous insulin – detemir versus NPH insulin					
HbA1c					
Montanana 2008 (PREDICTIVE-BMI)	HbA1c	**detemir**: 8.9 SD0.9 % **NPH**: 8.8 SD1.0 %	**detemir**: 7.8 SD1.1 % **NPH**: 7.8 SD1.0 %		p=NS
	percentage reaching HbA1c ≤7.0% without hypoglycaemia		**detemir**: 27% **NPH**: 27%		p=NS
hypoglycaemia					
Montanana 2008 (PREDICTIVE-BMI)	all hypoglycaemic events	not reported	26 weeks **detemir**: 256 **NPH**: 481	significantly less in detemir group, relative risk 0.62	p<0.0001
	patients reporting any hypoglycaemic events		26 weeks **detemir**: 34.7% **NPH**: 65.3%		
	nocturnal	not reported	26 weeks	significantly less in detemir	p<0.0001

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
	hypoglycaemic events		**detemir**: 46 **NPH**: 107	group, relative risk 0.43	
	patients reporting nocturnal hypoglycaemia		26 weeks **detemir**: 30.1% **NPH**: 69.9%		
	severe hypoglycaemic episodes		26 weeks **detemir**: 0 N**P**H: 3		
glycaemic excursions not reported					
total daily dose					
Montanana 2008 (PREDICTIVE-BMI)	insulin dose (IU/kg) – total (basal + bolus)	**detemir**: 0.64 SD0.21 IU/kg **NPH**: 0.59 SD0.18 IU/kg	**detemir**: 1.05 SD0.40 IU/kg **NPH**: 0.85 SD0.29 IU/kg		p value not reported
	insulin dose (IU/kg) – basal	**detemir**: 0.30 SD0.11 IU/kg **NPH**: 0.28 SD0.09 IU/kg	**detemir**: 0.59 SD0.25 IU/kg **NPH**: 0.47 SD0.18 IU/kg		p value not reported
weight change					
Montanana 2008 (PREDICTIVE-BMI)	weight change	**detemir**: 79.5 kg **NPH**: 82.2 kg	26 weeks **detemir**: +0.4 kg **NPH**: +1.9 kg	baseline-adjusted difference 1.5 kg (95% CI : 0.8, 2.8)	p<0.0001
	BMI	**detemir**: 31.6 kg/m2 **NPH**: 32.2 kg/m2	26 weeks **detemir**: +0.17 kg/m2 **NPH**: +0.77 kg/m2	baseline-adjusted difference 0.6 kg/m2	p<0.0001
	percentage with no change or loss of weight		26 weeks **detemir**: 46.4% **NPH**: 22.6%		p not reported
complication rates not reported					
adverse events					

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
Montanana 2008 (PREDICTIVE-BMI)	all adverse events		26 weeks **detemir**: 91 **NPH**: 73		
	serious adverse events		26 weeks **detemir**: 6 **NPH**: 4		all thought to be unlikely to be related to basal insulin
	withdrawals because of adverse events		**detemir**: 3 **NPH**: 0		
HR QoL	not reported				
insulin-naïve, oral antihyperglycaemics – detemir versus NPH insulin					
HbA1c					
Philis-Tsimikas 2006	HbA1c (%)	**morning detemir**: 9.08 SD0.97 % **evening detemir**: 8.88 SD0.95 % **NPH insulin**: 9.15 SD1.0 %	**morning detemir**: 7.50 SD0.96 % **evening detemir**: 7.40 SD0.77 % **NPH insulin**: 7.35 SD0.93 %	**morning detemir**: -1.58 SD1.07 % **evening detemir**: -1.48 SD1.01 % **NPH insulin**: -1.74 SD1.08 %	p=NS
hypoglycaemia					
Philis-Tsimikas 2006	major episodes		**morning detemir**: 0 **evening detemir**: 2 events in 2 (1.2%) patients **NPH insulin**: 0		too few events for statistical analysis
	all confirmed episodes		**morning detemir**: 91 events in 32 (19.4%) patients **evening detemir**: 82 events in 27 (16.0%) patients **NPH insulin**: 153 events in 53 (32.3%) patients	RR morning versus evening detemir: 1.43 morning detemir versus evening NPH: 0.68 evening detemir versus evening NPH: 0.47	morning detemir versus evening detemir or NPH p=NS; evening detemir versus evening NPH p=0.019
	nocturnal episodes		**morning detemir**: 6 events in	RR	morning detemir versus

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
			4 (2.4%) patients **evening detemir**: 19 events in 8 (4.7%) patients **NPH insulin**: 47 events in 22 (13.4%) patients (no major episodes occurred)	morning versus evening detemir: 0.35 morning detemir versus evening NPH: 0.13 evening detemir versus evening NPH: 0.35	evening detemir p=NS; morning detemir versus evening NPH p<0.001; evening detemir versus evening NPH p=0.031
glycaemic excursions					
Philis-Tsimikas 2006	pre-breakfast self-measured plasma glucose (mmol/L)		**morning detemir**: 7.97 SD1.23 mmol/L **evening detemir**: 6.50 SD1.28 mmol/L **NPH insulin**: 6.78 SD1.26 mmol/L		p<0.001 morning detemir versus evening detemir and evening NPH
	pre-dinner self-measured plasma glucose (mmol/L)		**morning detemir**: 7.11 SD1.91 mmol/L **evening detemir**: 7.76 SD1.84 mmol/L **NPH insulin**: 7.95 SD1.98 mmol/L		p=0.005 morning detemir versus evening detemir; p<0.001 morning detemir versus evening NPH
	9-point self-measured plasma glucose profile				similar for 2 evening insulin groups, mean profile of morning insulin detemir group was characterised by lower glycaemic values in the daytime and higher values overnight (p<0.001)
total daily dose					
Philis-Tsimikas 2006	mean insulin dose		**morning detemir**: 0.5 SD0.3 U/kg **evening detemir**: 0.4 SD0.2 U/kg **NPH insulin**: 0.4 SD0.2 U/kg		p=NS

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
weight change					
Philis-Tsimikas 2006	weight gain			**morning detemir**: +1.2 kg **evening detemir**: +0.7 kg **NPH insulin**: +1.6 kg	morning detemir versus evening detemir or NPH p=NS; evening detemir versus evening NPH p=0.005
complication rates not reported					
adverse events					
Philis-Tsimikas 2006	withdrawals due to adverse events		**morning detemir**: 2.4% **evening detemir**: 2.4% **NPH insulin**: 2.4%		
	overall profiles of adverse events		**morning detemir**: 123 AEs in 70 patients **evening detemir**: 150 AEs in 67 patients **NPH insulin**: 144 AEs in 82 patients		statistically similar, mostly considered unrelated to study insulins; all serious adverse events unrelated to insulins
	injection site reactions		**morning detemir**: 2 events in 2 patients **evening detemir**: 7 events in 6 patients **NPH insulin**: 2 events in 2 patients		p=NS
	potential allergic reactions		**morning detemir**: 2 events in 2 patients **evening detemir**: 5 events in 5 patients **NPH insulin**: 1 event in 1 patient		p=NS
HR QoL not reported					

4.4.15 Glycaemic control

None of the trials found any significant difference between HbA1c values between insulins glargine or detemir and NPH insulin at study end. HbA1c levels decreased by between 0.92 and 1.74% from baseline to study end. No significant difference between glargine and NPH was seen in the LEAD trial for patients reaching the HbA1c target (<7.5%, 38% for glargine, 30% for NPH) or the FBG target (≤6.7 mmol/L, 62% for glargine, 59% for NPH). There was a significant difference in the proportion of patients reaching the HbA1c target (<7.5%) without nocturnal hypoglycaemia in favour of glargine (23% for glargine, 14% for NPH, p=0.017). There was no significant difference between detemuir and NPH for patients reaching HbA1c ≤7.0% in the PREDICTIVE-BMI trial (27% of patients in each group).

The results of the meta-analysis are shown in Figure 2 for insulin glargine and in Figure 3 for insulin detemir. Baseline HbA1c values in the trials included in the meta-analysis were between 8.5 and 9.7% in the glargine versus NPH trials and between 7.8 and 9.2% in the detemir versus NPH trials. None of the meta-analyses showed a significant effect for insulin glargine (nine studies) or insulin detemir (four studies) versus NPH for HbA1c. The weighted mean difference was 0.00% (95% CI: -0.11, 0.10) for glargine and 0.07% (95% CI: -0.03, 0.18) for detemir. There was significant heterogeneity for the results for insulin glargine which disappeared when the only study of patients on previous insulin therapy (Rosenstock 2001)159 was excluded.

Figure 2: HbA1c glargine versus NPH

	glargine			NPH				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Eliaschewitz 2006	7.65	1.3	231	7.78	1.29	250	10.4%	-0.13 [-0.36, 0.10]
Fritsche 2003	8.1	1.3	227	8.3	1.3	232	10.1%	-0.20 [-0.44, 0.04]
HOE 901/2004 2003	8.98	1.5	64	8.68	1.4	68	3.7%	0.30 [-0.20, 0.80]
Massi Benedetti 2003	8.54	1.2	289	8.52	1.1	281	12.6%	0.02 [-0.17, 0.21]
Pan 2007	8.03	1.2	220	8.28	1.2	223	10.8%	-0.25 [-0.47, -0.03]
Riddle 2003	6.96	0.9	367	6.97	0.9	389	16.1%	-0.01 [-0.14, 0.12]
Rosenstock 2001	8.19	1.2	259	7.91	1.2	259	11.6%	0.28 [0.07, 0.49]
Wang 2007	7.62	0.98	16	7.43	0.73	8	2.0%	0.19 [-0.51, 0.89]
Yki-Järvinen 2000	8.34	0.92	214	8.24	0.92	208	13.3%	0.10 [-0.08, 0.28]
Yki-Järvinen 2006	7.14	0.63	61	7.16	0.73	49	9.3%	-0.02 [-0.28, 0.24]
Total (95% CI)			**1948**			**1967**	**100.0%**	**-0.00 [-0.11, 0.10]**

Heterogeneity: Tau² = 0.01; Chi² = 18.81, df = 9 (P = 0.03); I² = 52%
Test for overall effect: Z = 0.02 (P = 0.99)

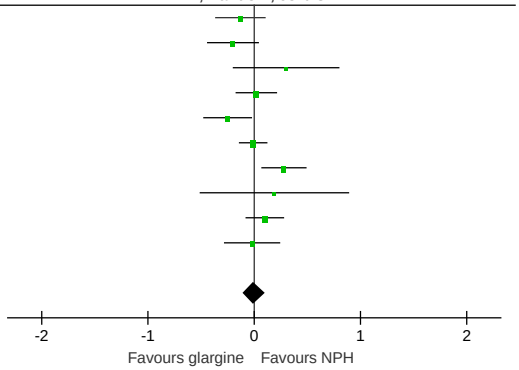
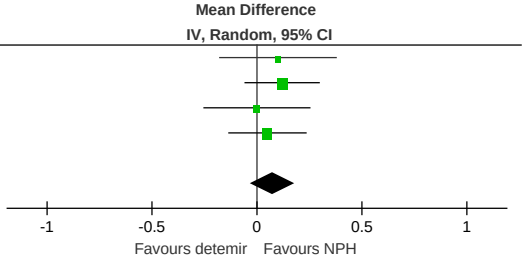


Figure 3: HbA1c detemir versus NPH

	detemir			NPH				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Haak 2005	7.6	1.85	341	7.5	1.28	164	14.4%	0.10 [-0.18, 0.38]
Hermansen 2006	6.58	0.99	237	6.46	0.97	238	35.5%	0.12 [-0.06, 0.30]
Montanana 2008	7.8	1.1	125	7.8	1	146	17.4%	0.00 [-0.25, 0.25]
Philis-Tsimikas 2006	7.4	0.77	169	7.35	0.93	164	32.7%	0.05 [-0.13, 0.23]
Total (95% CI)			**872**			**712**	**100.0%**	**0.07 [-0.03, 0.18]**

Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 3 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)



4.4.16 Hypoglycaemia

The LEAD trial and the PREDICTIVE-BMI trial found significant results in favour of glargine and detemir respectively in comparison with NPH for all hypoglycaemia-related outcomes reported. The trial by Wang 2007 found significantly fewer episodes of nocturnal hypoglycaemia with glargine compared to NPH, but no significant difference for all

hypoglycaemic events. The trial by Philis-Tsimikas 2006 found significant effects in favour of detemir for all comparisons of evening detemir versus evening NPH, but not for some of the other comparisons.

In the LEAD trial, there were 682 hypoglycaemic episodes in the glargine group had compared with 1019 in the NPH group (p<0.004). There were 515 episodes of symptomatic hypoglycaemia in the glargine group compared with 908 in the NPH group (p<0.0003), 5 of severe hypoglycaemia in the glargine group compared with 28 in the NPH group (p<0.03), and 221 episodes of nocturnal hypoglycaemia in the glargine group compared with 620 in the NPH group (p<0.001).

In the trial by Wang 2007, there were two hypoglycaemic events in two patients in the glargine group and six hypoglycaemic events in four patients in the NPH group (p=NS). There was one nocturnal hypoglycaemic event in one patient in the glargine group and four nocturnal hypoglycaemic events in four patients in the NPH group (p=0.028)

The PREDICTIVE-BMI trial reported significantly fewer hypoglycaemic events with detemir than with NPH (256 versus 481, relative risk 0.62, p<0.0001) and also significantly less nocturnal hypoglycaemia (46 versus 107, relative risk 0.43, p<0.0001).

In the trial by Philis-Tsimikas 2006 there were too few major hypoglycaemic episodes for statistical analysis (only two events in the evening detemir group). For all confirmed hypoglycaemic episodes, there were 91 events in 32 patients on morning detemir, 82 events in 27 patients on evening detemir, and 153 events in 53 patients on evening NPH, with a significant difference in favour or evening detemir versus evening NPH, but not of morning detemir versus evening detemir or NPH. For nocturnal hypoglycaemia, there were 6 events in 4 patients on morning detemir, 19 events in 8 patients on evening detemir, and 47 events in 22 patients on evening NPH, with a significant difference in favour or either detemir group versus evening NPH, but not of morning detemir versus evening detemir.

The meta-analyses for severe hypoglycaemia (Figure 4 and Figure 5) included six studies (reporting the number of patients with severe hypoglycaemia) for insulin glargine versus NPH and four studies for insulin detemir versus NPH. There was no significant difference in the number of patients with severe hypoglycaemia in the glargine or detemir groups compared to NPH insulin (relative risk 0.82 (95% CI: 0.45, 1.49) for glargine and relative risk 0.59 (95% CI: 0.15, 2.24) for detemir). There was no significant heterogeneity.

Figure 4: Severe hypoglycaemia glargine versus NPH

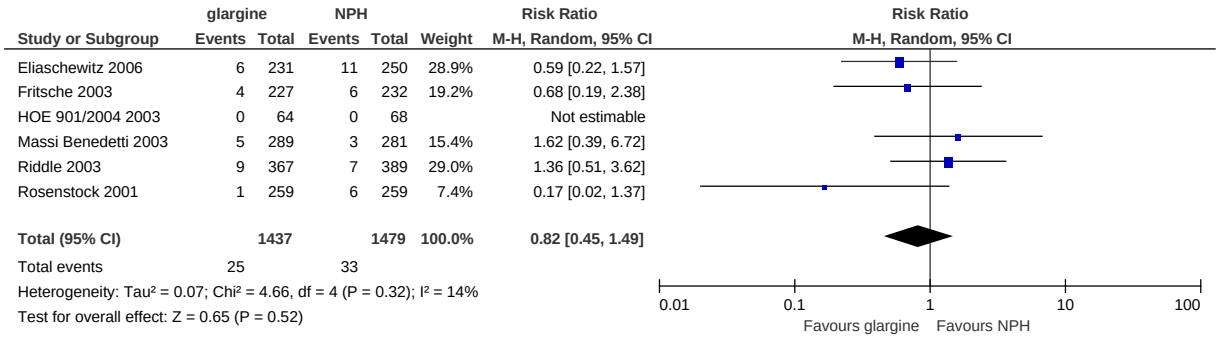
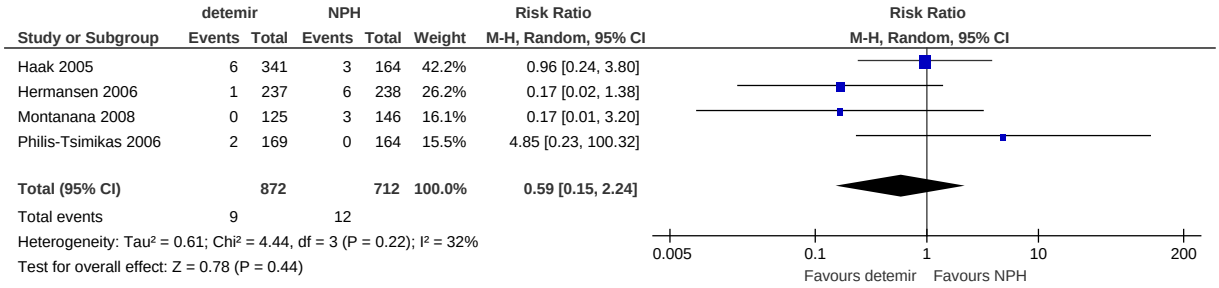


Figure 5: Severe hypoglycaemia detemir versus NPH



The meta-analysis for overall hypoglycaemia (Figure 6 and Figure 7) included seven studies (reporting the number of patients with any hypoglycaemia) for insulin glargine versus NPH and four studies for insulin detemir versus NPH. There was a significant difference in the number of patients reporting any hypoglycaemia in favour of the glargine and detemir groups compared to NPH insulin (relative risk 0.89 (95% CI: 0.83, 0.96, p=0.002) for glargine and relative risk 0.68 (95% CI: 0.54, 0.86, p=0.001) for detemir). There was no significant heterogeneity for glargine versus NPH but there was for detemir versus NPH (p=0.002).

Figure 6: Overall hypoglycaemia glargine versus NPH

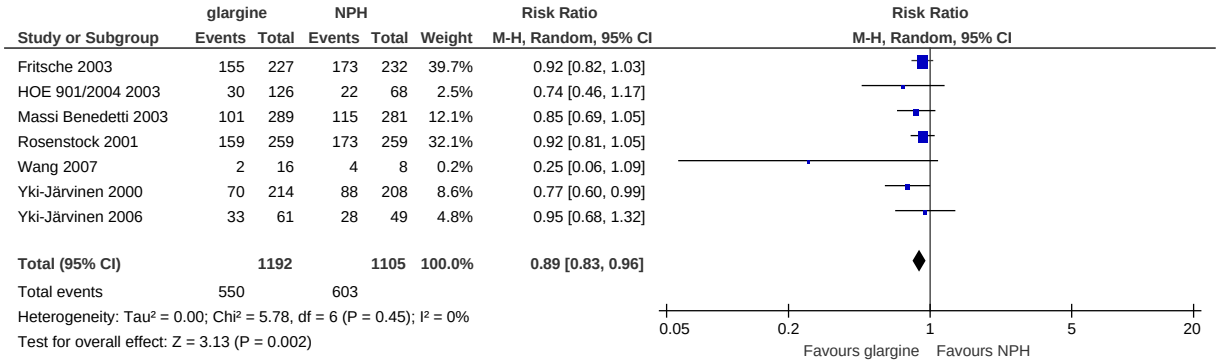
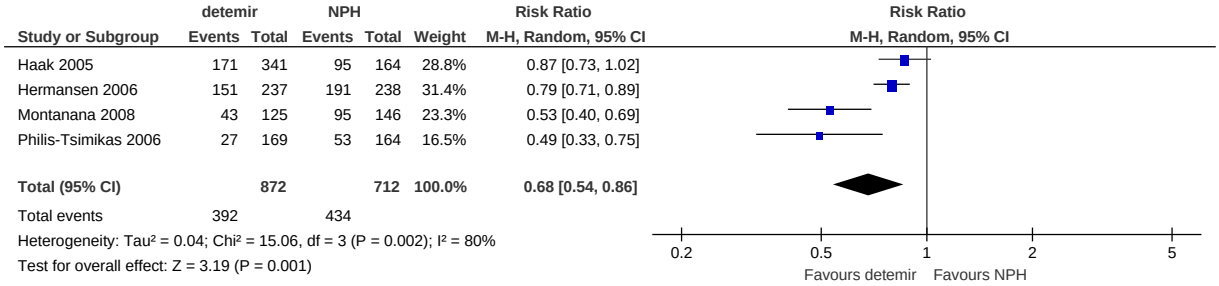
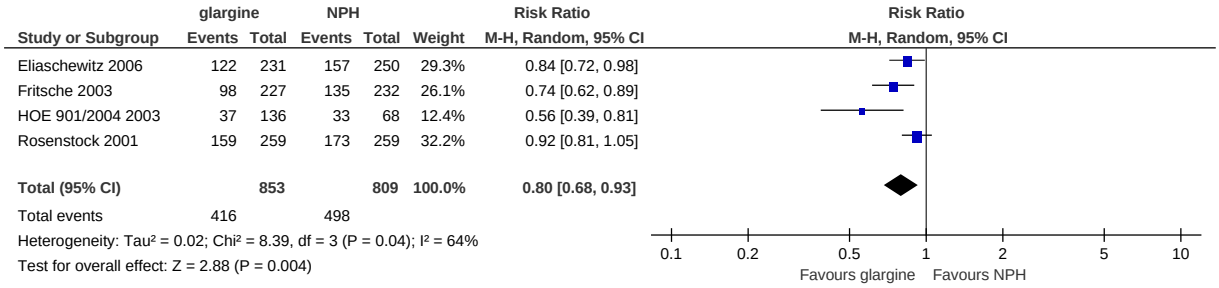


Figure 7: Overall hypoglycaemia detemir versus NPH



The meta-analysis for symptomatic hypoglycaemia (Figure 8) included four studies (reporting the number of patients with symptmatic hypoglycaemia) for insulin glargine versus NPH. There was a significant difference in the number of patients reporting symptomatic hypoglycaemia in favour of the glargine groups compared to NPH insulin (relative risk 0.80 (95% CI: 0.68, 0.93, p<0.004)). There was significant heterogeneity (p=0.04).

Figure 8: Symptomatic hypoglycaemia glargine versus NPH



The meta-analysis for nocturnal hypoglycaemia (Figure 9 and Figure 10) included seven studies (reporting the number of patients with nocturnal hypoglycaemia) for insulin glargine versus NPH and four studies for insulin detemir versus NPH. There was a significant difference in the number of patients reporting nocturnal hypoglycaemia in favour of the glargine and detemir groups compared to NPH insulin (relative risk 0.54 (95% CI: 0.43, 0.69, p<0.00001) for glargine and relative risk 0.54 (95% CI: 0.24, 0.68, p<0.00001) for detemir). There was significant heterogeneity for glargine versus NPH (p=0.03) but not for detemir versus NPH. The heterogeneity disappeared when the only study of patients on previous insulin therapy (Rosenstock 2001)[159] was excluded.

Figure 9: Nocturnal hypoglycaemia glargine versus NPH

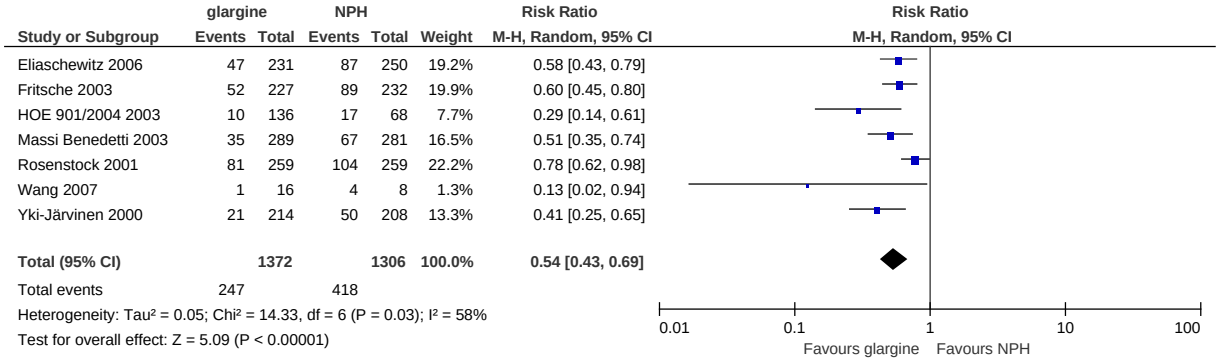
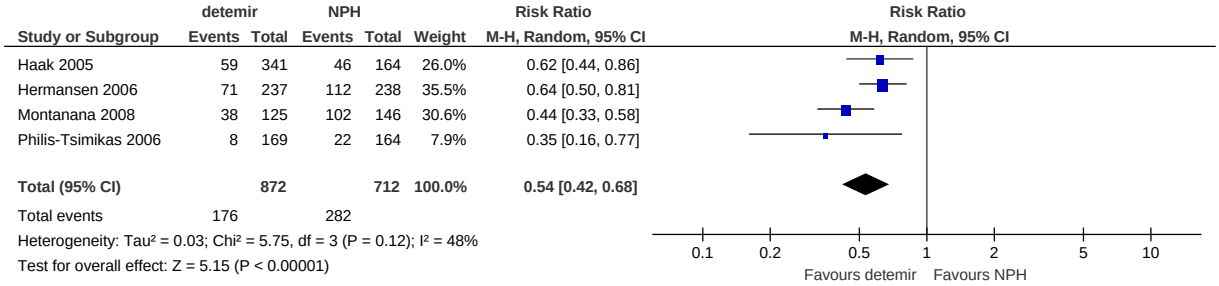


Figure 10: Nocturnal hypoglycaemia detemir versus NPH



4.4.7 Glucose excursions

The LEAD trial found eight-point blood glucose profiles to be similar between groups at study end, except for post-dinner values, where blood glucose concentration in the glargine group was significantly lower than in the NPH group (236 mg/dL versus 249 mg/dL, p=0.044).

In the Wang 2007 trial, a continuous glucose monitoring system was used. No differences between glargine and NPH were foung in average blood glucose values, pre-breakfast, 2 h

post-breakfast, pre-lunch, 2 h post-lunch, and 2 h post-supper blood glucose values, but the standard deviations of blood glucose, fasting plasma glucose and bedtime plasma glucose were significantly smaller with glargine compared to NPH, pre-supper and bedtime blood glucose values were significantly lower with glargine than NPH, and 3 am blood glucose values were significantly larger with glargine than NPH.

In the trial by Philis-Tsimikas, nine-point blood glucose profiles were similar for the two evening insulin groups, whereas the mean profile of the morning insulin detemir group was characterised by lower glycaemic values in the daytime and higher values overnight ($p<0.001$). Pre-breakfast plasma glucose values were between 1.19 and 1.47 mmol/L higher ($p<0.001$) in the morning detemir group, and pre-dinner plasma glucose values between 0.65 and 0.84 mmol/L lower ($p\leq0.01$) in the morning detemir group than in the evening groups.

4.4.8 Total daily insulin dose

No significant differences in mean daily insulin doses between treatment groups were reported in the LEAD trial, the trial by Wang 2007, the PREDICTIVE-BMI trial, or the trial by Philis-Tsimikas 2006.

4.4.9 Weight change

In the LEAD trial, BMI increased both in the glargine and in the NPH group to a similar extent during the course of the trial (+1.4 and +1.3 kg/m2). Similarly, in the trial by Wang 2007 body weight increased to a similar extent in both groups (+1.47 kg with glargine and +1.20 kg with NPH).

In the PREDICTIVE-BMI trial, significantly less weight gain was seen with insulin detemir than with NPH insulin over the course of the trial (+0.4 kg versus +1.9 kg, $p<0.0001$). Similarly, patients in the detemir group had a significantly smaller increase in BMI (+0.17 kg/m2 versus +0.77 kg/m2, $p<0.0001$).

In the trial by Philis-Tsimikas 2006, patients in the morning detemir group gained a mean of 1.2 kg, patients in the evening detemir group gained a mean of 0.7 kg, and patients in the evening NPH group gained a mean of 1.6 kg, with weight gain being significantly less in the evening detemir group than in the evening NPH group ($p=0.005$, no other significant differences).

Overall (eight studies), the glargine groups gained 0.23 kg less weight than the NPH groups (range 1.10 to +0.23 kg). However, a meta-analysis could not be carried out for this outcome because of too many missing standard deviations. The detemir groups (four studies) gained 1.20 kg less weight than the NPH groups (range 0.8 to -1.6 kg), but again a meta-analysis could not be carried out due to too many missing standard deviations.

4.4.10 Diabetic complications

Reported by none of the trials.

4.4.11 Adverse events

The LEAD study reported 66 adverse events in 45 patients that were possibly treatment related (22 patients in the glargine group and 23 patients in the NPH group). The majority was related to injection-site reactions, and although p-values were not reported, there does not seem to have been a significant difference between groups. There was no significant difference in serious adverse events between groups, and none of the events were considered unusual for the demographic group studied (i.e. not related to the treatment).

The trial by Wang 2007 did not report adverse events.

In the PREDICTIVE-BMI trial, there were 91 adverse events in the detemir group and 73 in the NPH group, six of these in the detemir group and four in the NPH group were serious (but thought to be unlikely to be related to basal insulin). There were three withdrawals because of adverse events in the detemir group and none in the NPH group.

In the trial by Philis-Tsimikas 2006, there was no significant difference in overall adverse events between comparison groups (123 to 144 events in 67 to 82 patients in each group). No serious adverse events were considered to be related to the insulins. There was no significant difference in potential allergic reactions (1 to 5 events in 1 to 5 patients per group) or injection site reactions (2 to 7 events in 2 to 6 patients per group) between the groups.

4.4.12 Health-related quality of life

Reported by none of the trials.

4.4.13 Glargine versus detemir

Table 22: Main results of included trial - glargine versus detemir

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
insulin-naïve– glargine versus detemir					
HbA1c					
Rosenstock 2008	HbA1c (%)	**detemir (n=291)**: 8.64 SD0.78 % **glargine (n=291)**: 8.62 SD0.77 %	**detemir (n=268)**: 7.16 SE0.08 % **glargine (n=275)**: 7.12 SE0.08 %	difference glargine – detemir 0.05% (95% CI: 0.11, 0.21)	p=NS
	patients achieving HbA1c ≤7.0% (%)		**detemir (n=248)**: 52% **glargine (n=259)**: 52%		p=NS
	patients achieving target HbA1c ≤7.0% (%) without hypoglycaemia (%)		**detemir (n=248)**: 33% **glargine (n=259)**: 35%		p=NS
Hypoglycaemia					
Rosenstock 2008	all hypoglycaemic episodes		**detemir**: participants: 182 (63%) episodes: 1521 rate: 5.8 per patient-yr **glargine**: participants: 191 (66%) episodes: 1670 rate: 6.2 per patient-yr	relative risk 0.94 (95% CI: 0.71, 1.25)	p=NS

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
	nocturnal hypoglycaemic episodes		**detemir**: participants: 95 (33%) episodes: 352 rate: 1.3 per patient-yr **glargine**: participants: 93 (32%) episodes: 350 rate: 1.3 per patient-yr	relative risk 1.05 (95% CI: 0.69, 1.58)	p=NS
	major hypoglycaemic episodes		**detemir**: participants: 5 (2%) episodes: 9 rate: 0.0 per patient-yr **glargine**: participants: 8 (3%) episodes: 8 rate: 0.0 per patient-yr		not reported, number too small
	major nocturnal hypoglycaemic episodes		**detemir**: participants: 3 (1%) episodes: 5 rate: 0.0 per patient-yr **glargine**: participants: 4 (1%) episodes: 4 rate: 0.0 per patient-yr		not reported, number too small
	minor hypoglycaemic episodes		**detemir**:	relative risk 1.05 (95% CI: 0.75,	p=NS

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
			participants: 135 (46%) episodes: 737 rate: 2.9 per patient-yr **glargine**: participants: 151 (52%) episodes: 786 rate: 2.9 per patient-yr	1.46)	
	minor nocturnal hypoglycaemic episodes		**detemir**: participants: 73 (25%) episodes: 212 rate: 0.8 per patient-yr **glargine**: participants: 71 (24%) episodes: 192 rate: 0.7 per patient-yr	relative risk 1.17 (95% CI: 0.75, 1.83)	p=NS
	symptoms only hypoglycaemic episodes		**detemir**: participants: 137 (47%) episodes: 760 rate: 3.0 per patient-yr **glargine**: participants: 133 (46%) episodes: 866	relative risk 0.88 (95% CI: 0.61, 1.25)	p=NS

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
			rate: 3.2 per patient-yr		
	symptoms only nocturnal hypoglycaemic episodes		**detemir**: participants: 48 (17%) episodes: 128 rate: 0.5 per patient-yr **glargine**: participants: 49 (17%) episodes: 151 rate: 0.6 per patient-yr	relative risk 0.88 (95% CI: 0.50, 1.54)	p=NS
glycaemic excursions					
Rosenstock 2008	within-participant variation (mmol/L) – pre-breakfast		**detemir** (n=238): SD1.06 **glargine** (n=257): SD1.03		p=NS
	within-participant variation (mmol/L) – pre-dinner		**detemir** (n=238): SD1.60 **glargine** (n=258): SD1.55		p=NS
total daily dose					
Rosenstock 2008	daily insulin dose		**detemir** (n=227): 0.78 U/kg/day (0.52 U/kg for once daily and 1.0 U/kg for twice daily, with 55% on twice daily) **glargine** (n=248): 0.44 U/kg/day		p-value not reported
weight change					

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
Rosenstock 2008	weight gain	**detemir**: 87.4 SD16.6 kg **glargine**: 87.4 SD17.4 kg		detemir (n=230): +3.0 SE0.4 kg glargine (n=252): +3.9 SE0.4 kg confirmed in ITT analysis; but weight gain with once daily detemir was +2.3 SE0.5 kg and with twice daily detemir +3.7 SE0.4 kg (no difference to glargine)	p=0.01
complication rates - not reported					
adverse events					
Rosenstock 2008	withdrawal because of adverse events		**detemir**: 8% **glargine**: 4%		
	serious advserse events		**detemir**: 42 patients with 47 events **glargine**: 53 patients with 73 events but only 5 events with detemir and 4 events with glargine considered to be (possibly) related to study medication		
	deaths		**detemir**: n=1 (possibly myocardial infarction) **glargine**: n=1 (pulmonary fibrosis)		
	injection site disorders		**detemir**: 4.5% **glargine**: 1.4%		
	allergic reactions		**detemir**: n=3 **glargine**: n=1		
	skin disorders (incl. pruritus and		**detemir**: n=6		

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
	rash)		**glargine**: n=1		
HR QoL - not reported					

The results of the trial by Rosenstock 2008 suggest that the effects of glargine and detemir are similar. After 52 weeks of treatment, there were no significant differences in HbA1c, percentage of patients reaching HbA1c ≤7.0% (with or without hypoglycaemia), overall hypoglycaemic events or nocturnal hypoglycaemic events. There was statistically significantly less weight gain with detemir overall than with glargine (+2.7 versus 3.5 kg, p=0.03), but the difference of 0.8 kg is of doubtful clinical significance. However, when analysing use of detemir once or twice daily, only the once daily detemir group was at an advantage for weight gain (+2.3 kg), whereas the weight gain in the twice daily detemir group was similar to that of the glargine group (+3.7 kg). The mean daily dose was higher for detemir (0.52 U/kg with once daily dosing, 1.00 U/kg with twice daily dosing) than for glargine (0.44 U/kg). Injection site reactions were slightly more common with detemir than with glargine (4.5% versus 1.4%, p-value not reported).

Another short study, available in abstract only[186] compared the effect of once daily glargine and detemir on blood glucose profiles over the course of a week, and found no significant difference.

4.5 Discussion

Taking the evidence from the systematic reviews and the randomised controlled trials as a whole, both insulin glargine and insulin detemir appear to be equivalent with respect to parameters of glycaemic control in comparison with NPH insulin. This was confirmed by our meta-analysis of trials included in previous meta-analyses and additional trials identified. A significant reduction in nocturnal hypoglycaemia was associated with both glargine and detemir treatment, but the effect size is not clear from the reviews. The reduction in nocturnal hypoglycaemia both for glargine and detemir was confirmed by our meta-analysis. Some reduction in overall or symptomatic hypoglycaemia was also seen with glargine or detemir, but this was not consistent for all trials. Our meta-analysis did however show a significant reduction in overall hypoglycaemia for both glargine and detemir and for symptomatic hypoglycaemia for glargine (not reported for detemir). In many trials, severe hypoglycaemia did not occur frequently enough to allow a meaningful statistical analysis.

Glycaemic excursions were reported infrequently but where reported, no consistent differences between glargine or detemir and NPH insulin were seen.

Total daily doses of insulin and health related quality of life (or patient satisfaction) were reported too infrequently to allow any conclusions.

Similarly, change in weight or BMI was not reported systematically enough to allow any firm conclusion. There was some indication that there may be less weight gain with the long acting analogues than with NPH insulin (possibly dependent on previous insulin treatment), but the results on this outcome were not consistent. One study of glargine versus detemir suggested that there may be less weight gain with once daily detemir than with once daily glargine. Most trials included in this review did not provide enough information to enable a meta-analysis, but data extracted also suggest that there may be slightly less weight gain with detemir than with glargine, though the difference is of doubtful clinical significance. Any effects seen appear to have been independent of whether patients have been treated with insulins previously or not, or were on oral anti-hyperglycaemic therapy or not.

Reported adverse events appear to have been largely similar between the long acting insulin analogues and NPH insulin, possibly with more injection site reactions for the analogues. However, no data on the longer term safety of the insulin analogues were available.

No information was available on diabetic complications, and the studies were underpowered to assess such outcomes or mortality reliably. Horvath and colleagues[141] reported limited data on a possible differential effect of glargine on development of clinically significant

macular oedema depending on previous treatment with insulin, suggesting that this may be a point of concern.

4.6 Conclusions

Glargine and detemir are equivalent to NPH in terms of glycaemic control as reflected in HbA1c, but have modest advantages in terms of hypoglycaemia, especially nocturnal.

There is little to choose between the two analogues. Detemir, when used once daily, may be associated with marginally less weight gain, but this is unlikely to be clinically significant. It requires a higher daily dose than glargine which will have cost implications.

5 Chapter 5 The glitazones

5.1 History

There are two thiazolidinediones, or glitazones for short, used in the UK – pioglitazone and rosiglitazone. They have been the subject of technology appraisals (TAs) by NICE, starting with appraisals of the individual drugs (TAs 9 and 21), later superseded by a review of both, TA 63 issued in August 2003.[12]

The guidance issued after the review in 2003 stated that;

"1.1 For people with type 2 diabetes, the use of a glitazone as second-line therapy added to either metformin or a sulphonylurea – as an alternative to treatment with a combination of metformin and a sulphonylurea – is not recommended except for those who are unable to take metformin and a sulphonylurea in combination because of intolerance or a contraindication to one of the drugs.

1.3 The present UK licence does not allow the Institute to recommend the use of glitazones in triple combination therapy, as monotherapy, or in combination with insulin."

Section 1.1 was based on cost-effectiveness rather than clinical efficacy. Regarding section 1.3, the Appraisal Committee noted (paragraph 4.3.6 of the guidance) that;

"..the off-licence use of glitazones as part of triple combination therapy is widely practised in the UK. This use has been particularly targeted at a subset of people with diabetes for whom the combination of metformin and sulphonylurea has failed to achieve target HbA1c levels despite appropriate doses of these drugs, and for whom the conventional choice of switching to insulin therapy is not acceptable…."

The Committee was aware of recent trial evidence on the clinical effectiveness of triple therapy. However NICE is restricted to issuing guidance on licensed indications and so could not comment.

The licensed indications have changed, and are now (based on EMEA 2008)[187];

Rosiglitazone is indicated in the treatment of type 2 diabetes

- As monotherapy in patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance.
- As dual oral therapy in combination with metformin in patients (particularly overweight ones) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin
- As dual oral therapy in combination with a sulphonylurea, only in patients who show intolerance to metformin, or for whom metformin is contraindicated, with insufficient glycaemic control despite sulphonylurea monotherapy
- As triple oral therapy in combination with metformin, in patients with insufficient glycaemic control despite dual oral therapy.

The license for pioglitazone is as above, but with in addition;[188]

- Pioglitazone is also indicated for combination with insulin in type 2 diabetes patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

There are now more trials than were available at the time of NICE TA 63. The evidence base for rosiglitazone was updated in a Cochrane review published in July 2007 by Richter and colleagues.[189] Their summary included;

"Eighteen trials randomised 3888 people to rosiglitazone therapy. The longest duration of rosiglitazone treatment was four years. Most trials lasted around half a year. Unfortunately, the published studies of at least 24 weeks rosiglitazone treatment in people with type 2 diabetes mellitus did not provide relevant evidence that patient-orientated outcomes are positively influenced by this agent. The chance of developing oedema was approximately doubled. The single large randomised controlled trial showed evidence of raised cardiovascular risk after rosiglitazone treatment. Moreover, new safety data show increased numbers of fractures in women."

The review noted an increased risk of myocardial infarction in those treated with rosiglitazone but that this was not statistically significant.

A Cochrane review of pioglitazone by the same authors[190] (published Cochrane Library Issue 4 2006) was summarised thus:

"Twenty-two trials which randomised 6200 people to pioglitazone treatment were identified. Longest duration of therapy was 34.5 months. Published studies of at least 24 weeks pioglitazone treatment in people with type 2 diabetes mellitus did not provide convincing evidence that patient oriented outcomes like mortality, morbidity, adverse effects, costs and health-related quality of life are positively influenced by this compound. Metabolic control measured by HbA1c as a surrogate endpoint did not demonstrate clinically relevant differences to other oral antidiabetic drugs. Occurrence of oedema was significantly raised."

Comments like this would apply to most new diabetes drugs, since trials are usually short-term and rely on proxy outcomes, usually HbA1c. There are few trials such as UKPDS which are long enough to produce data on complications or mortality. Nor are they usually long enough to produce data on uncommon side-effects.

The only exception to the short-term trials found in the Cochrane review was the PROactive study[191], which was a large study with over 500 patients which did set out to examine the effect of pioglitazone on hard outcomes, in a trial against placebo, in patients who had evidence of macrovascular disease. Patients continued their other diabetes medications, mainly metformin, sulphonylureas, insulin, or combinations thereof. The primary end-point was a composite of death and non-fatal cardiovascular outcomes. The pioglitazone group had a lower risk but this did not reach statistical significance (HR 0.90, 95% CI 0.80 to 1.02; p = 0.095) despite the large numbers of recruits and events (at least one end-point event in 514 of the pioglitazone group and 572 of the placebo group). A secondary endpoint measure of death, non-fatal MI and stroke did reach statistical significance: HR 0.84, 0.72-0.98; p=0.027. The closing statement focussed on the secondary outcome, which was another composite outcome;

"Pioglitazone reduces the composite of all-cause mortality, non-fatal MI and stroke"

However, oedema and heart failure were commoner in the pioglitazone group, with 11% reported as having heart failure compared to 8% in the placebo group; the proportions needing hospital admission were 6% and 4%. The death rates from heart failure showed no difference. Heart failure was not defined centrally, but was "as judged by the investigator". Another outcome was "oedema in the absence of heart failure". Heart failure can be difficult to diagnose, and the absence of any difference in mortality from heart disease, might suggest that it could have been over-diagnosed. However an independent group of cardiologists reviewed all the cases of serious heart failure and concluded that it did occur more frequently in the pioglitazone group (5.5% versus 4.2% for placebo) .[192]

The most relevant finding from PROactive, in the light of today's concerns about the safety of rosiglitazone, was that even if the reduction in cardiovascular events was small, it was certainly not increased by pioglitazone.

The results have been somewhat optimistically interpreted in later publications. The economic analysis reported that,[193]

"Within trial cost-effectiveness analysis: compared with pioglitazone was associated with improved life expectancy (undiscounted 0.0109 years)"

Note that 0.0109 years = 4 days.

Another finding from PROactive was that progression to needing insulin was halved in the pioglitazone group. At the start of the study, about one-third of the patients were on insulin. Their mean age was 62; mean BMI 31; and duration of diabetes 8 years. 75% had a history of hypertension. Mean HbA1c was around 7.8%. The protocol asked investigators to aim for an HbA1c of <6.5%. By the end of follow-up, 11% of the pioglitazone group and 21% of the placebo group were on insulin treatment. The switch to insulin started early in the trial, presumably due to investigators trying to achieve the HbA1c target.

Given that one alleged benefit of some of the new drugs for diabetes is a delay in, or avoidance of, insulin therapy, this finding seems highly relevant. The reduction in insulin use played a significant part in the economic analysis of the PROactive trial[193] where the CORE team with co-authors from the manufacturer, reported that adding pioglitazone was cost-effective.

5.2 Rosiglitazone and safety

The glitazones situation changed in May 2007, when a meta-analysis by Nissen and Wolski was published in NEJM.[194] It concluded that there was an increased risk (by 40%) of cardiovascular disease with rosiglitazone, compared to those on metformin or a sulphonylurea, or placebo. An editorial shortly after stated that a patient level analysis by the manufacturer of rosiglitazone had confirmed the findings.[195]

Much debate followed. Another meta-analysis involving adding a new trial, the RECORD study [196] to those in the meta-analysis by Nissen and Wolski, found that the risk still seemed to be increased, this time at an odds ratio of 1.33 (95% CI 1.02 to 1.72).[197] This was because the RECORD study interim analysis reported a hazard ratio of only 1.11.

It is worth noting that the absolute risk in the studies was low.

The meta-analysis by Nissen and Wolski was criticised on various grounds, in particular that it excluded six trials which had no relevant events. With no events, it is impossible to assess the relative cardiovascular risks. However, the lack of events can tell us something about absolute risks. Interestingly, of the 42 trials which were included, 26 were unpublished, with data obtained from trials provided by Glaxo Smith Kline to the US FDA. The FDA later (letter dated March 25th 2008)[198] complained to GSK about failure to pass on data from some trails and post-marketing studies.

A later meta-analysis (Diamond and colleagues)[199] applied different statistical techniques, included the six studies with no events, but excluded four studies. They then re-calculated the odds ratios in six different ways, and showed that while there was still an increased risk, for both MI and cardiovascular death, the confidence intervals now over-lapped with unity, and the odds ratios varied with method. For example the OR for cardiovascular death ranged from 1.58 (95% CI 0.91 to 2.74) to 1.16 (0.75 to 1.79).

The Nissen and Wolksi review included all trials, irrespective of duration.[194] Most were too short-term to assess cardiovascular outcomes, but used glycaemic control as the main outcome. Singh and colleagues [200] provided another meta-analysis, but restricted to trials

with at least 12 months of follow-up, and which reported cardiovascular events. Their inclusion criteria reduced the number of trials to only four. They found that rosiglitazone increased the risk of myocardial infarction (RR 1.42; 95% CI 1.06 to 1.91). It also doubled the risk of heart failure, as had been known. However, the overall cardiovascular mortality was not increased (RR 0.9; CI 0.63 to 1.26). The finding that heart failure is increased (with both glitazones) but that cardiovascular death was not, was also reported in yet another meta-analysis by Lago and colleages.[201]

The NICE GDG reviewed the evidence up to the end of 2007, including trials and statements from regulatory bodies, the EMEA, the FDA and the MHRA. It noted that the new glycaemic control studies did not change what was already known. The main issue was safety. The GDG commented in guideline CG66[6] that;

The GDG felt that there was certainly a "signal" of increased risk of non-fatal myocardial infarction for rosiglitazone"

(The term "signal" had been used by the FDA).

But that;

"On balance, despite reservations over rosiglitazone, it was not felt to be possible to unequivocally recommend a preference for pioglitazone in all circumstance, but rather to allow the choice of agent to rest with the person with diabetes and their advisor, taking account of the then regulatory advice (which may yet change)"

The GDG continued;

"However the issues over fracture and fluid retention/cardiac failure and the costs of these drugs led the GDG to conclude that the TZDs could not generally replace sulphonylureas as second line therapy, except where sulphonylureas were contraindicated by particular risk of hypoglycaemia."

However, the GDG then went on to note that;

"The health economic modelling appeared to identify that these drugs, in particular the then more highly priced rosiglitazone, were not cost-effective compared to insulin therapy."

but hypothesised that this might not apply in people of higher body weight where insulin resistance was marked and weight gain common with insulin treatment.

If a patient is going to receive a glitazone, the key issue is whether pioglitazone is safer than rosiglitazone. If so, the next GDG may wish to recommend that rosiglitazone should not be used.

5.2.1 Recent evidence

We found no new trials of glitazones with hard clinical outcomes which were not known to the previous guideline group.

We did find a trial which reported proxy outcomes. In the PERISCOPE, Nissen and colleagues [202] compared pioglitazone with glimepiride (a sulphonylurea) to see if there were any differences in progression of coronary artery disease. A total of 543 patients had coronary intravascular ultrasonography to measure the extent of coronary atherosclerosis, were randomised to pioglitazone or glimepride, and had their coronary investigation repeated 18 months later. The investigators were asked to try to achieve an HbA1c level of <7%. Baseline HbA1c levels were identical in the two group (7.4%), but over time, the glimepride group developed slightly higher levels – Hba1c 7.0% versus 6.9% (from text; figure 2 suggests that by study end the difference was about 0.3%).

The main outcome measure was the mean atheroma volume. This increased by 0.73% (95% CI 0.33% to 1.12%) in the glimepride group but decreased by 0.16% (-0.57 to + 0.25%) in the pioglitazone group. The clinical significance of this small difference is uncertain, and if the effect was due to the insulin-sensitising pioglitazone having advantages over the insulin secretagogue glimepiride, then as the accompanying editorial points out, the more cost-effective approach would have been to compare metformin with a sulphonylurea.[203]

A claim has been made recently that similar results have been obtained with rosiglitazone. These come from an unpublished trial, called VICTORY (Vein-Coronary Atherosclerosis and Rosiglitazone after bypass surgery). The results were presented at the American College of Cardiology 2008 conference, and the claim is reported in a newsletter , Heartwire (April 10th).[204] The data reported are of atheroma plaque volume, with a smaller percentage increase in those on rosiglitazone, compared to those on placebo. Two comments are necessary. Firstly, atheroma increased in both groups. Secondly, the different was not statistically significant (the p value was 0.22). Further assessment must await full publication, but the details available at present do not justify the claim that the effect of rosiglitazone is similar to those seen with pioglitazone in PERISCOPE.

As reported in the recent guideline, a meta-analysis of the risk of cardiovascular events with pioglitazone was carried out by Lincoff and colleagues (who include Nissen and Wolski, who did the similar meta-analysis for rosiglitazone).[205] Based on 19 trials with 16,930 participants, they concluded that pioglitazone was associated with a reduced risk of death, myocardial infarction or stroke. They speculate that the differences in cardiovascular risk between rosiglitazone and pioglitazone are related to different effects on blood lipids (pioglitazone having a greater reduction in triglycerides and an increase in HDL cholesterol).

This meta-analysis included only trials funded by the manufacturer, because the authors used patient level data obtained from Takeda. Because most trials were short term and had relatively small numbers, around 80% of the events came from the PROactive trial.

5.2.2 Fractures

In the PERISCOPE trial, fractures occurred in 3% of the pioglitazone group but in none of the sulphonylurea group (p = 0.004).

Fracture risk has been reported in other studies. Kahn and colleagues[29] in the “durability” study (ADOPT) reported that 9.3% of women on rosiglitazone had fractures compared to 5.1% on metformin and 3.5% on glibenclamide. The increases were in fractures of upper limb and foot, rather than in the classical osteoporosis-associated neck of femur and vertebrae. There was no difference in men.

A case/control study by Meier and colleagues[206] using British general practice data from GPRD also found that use of glitazones was associated with increased fracture rates. No such increase was seen with other oral diabetes drugs.

A letter to physicians issued by Takeda Pharmaceuticals, and posted on the US Food and Drug Administration website[207] reported an analysis of its clinical trials database on pioglitazone. They compared the incidence of fractures in over 8100 patients treated with pioglitazone compared to over 7400 patients treated with a comparator.

The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on pioglitazone is therefore 0.8 fractures per 100 patient years of use. There was no increased risk of fracture identified in men.

The letter stated “the risk of fracture should be considered in the care of female patients with type 2 diabetes mellitus who are currently being treated with pioglitazone, or when initiation of pioglitazone treatment is being considered”.

5.3 What have other organisations said about rosiglitazone?

The FDA convened an advisory committee which concluded that,[208]

“The use of rosiglitazone for the treatment of type 2 diabetes was associated with a greater risk of myocardial ischemic events that placebo, metformin or sulphonylurea”

However, the advisory committee did not recommend that rosiglitazone be removed from the market. It asked for label warnings, educational efforts and further trials.

The FDA issued a statement on November 14th 2007, with the key message being as follows.[209]

- **A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), moast of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients) comparing Avandia to some other approved oral antidiabetic agents, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.**

Health Canada issued a warning letter announcing new restrictions on the use of rosiglitazone on November 6th 2007, the key messages being;[210]

- **Rosiglitazone is no longer approved for use alone to treat type 2 diabetes, except when metformin use is contraindicated or nor tolerated**
- **Rosiglitazone is no longer approved for use with a sulfonylurea drug (such as glyburide) except when metformin is contraindicated or not tolerated**
- **Rosiglitazone should not be used if you have heart failure, or have experienced heart failure in the past**
- **Patients who are taking rosiglitazone, especially those with underlyng heart disease, or those who are at high risk of heart attack or heart failure, should talk to their doctor about the benefits and risks of continuing rosiglitazone therapy**
- **Rosiglitazone should not be taken if you are using insulin**
- **Rosiglitazone should not be used in “triple therapy”**

These restrictions were based on advice from the Scientific Advisory Committee on metabolic and endocrine therapies (SAC-MET). The minutes of the meeting on November 16th 2007 give little detail for confidentiality reasons, but one comment was;[211]

“The Committee expressed concern that the risk data on rosiglitazone were inconclusive.”

The recommendations are curious, in that they say that rosiglitazone can be used when metformin cannot, but do not mention pioglitazone. Given that the evidence suggests cardiovascular harm with rosiglitazone but benefit with pioglitazone, they might have suggested that if metformin was not tolerated, pioglitazone should be the glitazone of choice.

The Drug and Therapeutics Bulletin reassessed the glitazones in April 2008.[212] As regards glycaemic control, the conclusions were;

- that the glitazones were useful in dual combination with metformin or a sulphonylurea in patients who could not tolerate one or other of those
- that there was no convincing evidence of any benefits over metformin or a sulphonylurea as monotherapy

- that evidence for their use in triple therapy was weak, and that they should be reserved for patients in whom insulin was contraindicated or poorly tolerated
- that if a glitazone was thought to be necessary, pioglitazone was probably safer.

Two other UK bodies have issued advice.

The Midlands Therapeutics reviews and Advisory Committee (MTRAC) reviewed both rosiglitazone and pioglitazone in March 2008.[213,214] They concluded that rosiglitazone should not be used;

"Rosiglitazone cannot be recommended for prescribing, based on the current concerns about potential cardiovascular adverse effects and the lack of evidence for improved patient-oriented outcomes."

Pioglitazone glitazone was classed as suitable for restricted prescribing, but with a low place in therapy.

The diabetes managed clinical network for Great Glasgow and Clyde, as reported in the Scotsman of 8th May[215], has recommended that no new patients should be started on rosiglitazone, and that GPs should look carefully at those already taking it. Some consultants favoured withdrawing rosiglitazone completely.

The consensus group from ADA and EASD[216] issued an update about the glitazones to its alogorithm on treatment for type 2 diabetes. The update reserved judgement;

"At this time, we do not view as definitive the clinical trial data regarding increased or decreased riskof myocardial infarctions with rosiglitazone or pioglitazone, respectively.

On the other hand, we do believe that the weight of the new information …should prompt clinicians to consider more carefully whether to use this class of drugs versus insulin or sulfonylureas…"

and

"The current decision not to remove either or both of the gltiazones from the algorithm represents a balance between the preservations of options to treat a challenging and progressive disease, and the recent unfavourable evidence"

The Australian National Prescribing Service issued notes on rosiglitazone in December 2007[217] and on pioglitazone in March 2008.[218] They also issued a media release in December 2007 saying that;[219]

"Prescribers should also be aware of a possible increased risk of myocardial ischaemia in patients taking rosiglitazone. The same risk has not been shown with pioglitazone but the possibility cannot be dismissed".

The December note on rosiglitazone suggested that in patients failing on dual therapy, clinicians should consider using insulin rather than rosiglitazone because;

- *insulin reduces the risk of diabetic complications, whereas the effect of rosiglitazone on diabetes-related morbidity and mortality is still unclear*
- *the long-term safety profile of insulin is better defined. The only completed long term trial of rosiglitazone reported significantly higher rates of heart failure, oedema and fracture amongst the rosiglitazone group than among those using metformin or glibenclamide.*
- *Greater reductions in HbA1c levels have been reported among patients with poor glycaemic control who were treated with insul n rather than rosiglitazone."*

The pioglitazone note in March 2008 was quite similar. Neither note suggested that pioglitazone should be preferred to rosiglitazone. A practice review for GPs dated February 2008 suggested that;[220]

"If metformin and a sulphonylurea no longer control blood glucose, start insulin promptly. Trialling a glitazone as part of triple oral therapy may be an option but insulin should be started if hyperglycaemia is still uncontrolled after 3 months."

More on glitazones safety.

As new trials are reported, they are being added to new meta-analyses. Dahabreh[221] updated the Nissen 2007[194] meta-analysis with the results from the DREAM[222] and ADOPT[29] trials, and the interim report from the RECORD trial.[196] (NB. DREAM was in patients with IGT or IFG, not diabetes). He noted the debate about the methods for doing meta-analysis when some trials had no events, and did the analyses using methods which allowed inclusion of such trials, as well as using the Peto method used in the original Nissen meta-analysis.

The results were consistent with the previous finding of an increase in myocardial infarction with rosiglitazone, but ORs were slightly less and in two of the five meta-analyses their CIs sometimes just overlapped with no increase (95% CIs of 0.97 – 1.59 and 0.96 – 1.57).

It is curious that rosiglitazone appears to increase non-fatal MI but not cardiovascular death. It may simply be a function of numbers, because the CV death ORs have much wider CIs.

Another meta-analysis by Mannucci and colleagues[174] included 84 published and 10 unpublished trials of pioglitazone compared to placebo or active comparators, but excluded the PROACTIVE trial. They reported a reduction of all-cause mortality with pioglitazone (OR 0.30; 95% CI 0.14 – 0.63: $p < 0.05$), but no significant effect on non-fatal coronary events.

Several new studies have asked why rosiglitazone should increase cardiovascular events but pioglitazone does not. Most have concluded that the likely reason is that while the two glitazones have the same effects on glycaemic control, and the same side-effects of fluid retention and heart failure, they have different effects on blood lipids. Berneis and colleagues[223] (based on data from the abstract only) carried out a very small cross-over trial in 9 patients, giving them all 12 weeks on pioglitazone and 12 weeks on rosiglitazone. Total cholesterol increased more on rosiglitazone (need absolute levels) than on pioglitazone ($p = 0.04$), and triglycerides increased on rosiglitazone but decreased on pioglitazone ($p = 0.004$).

Chappuis and colleagues[224] also studied patients on both glitazones, this time with 17 patients having 12 weeks on each. The effects of HbA1c were similar, but triglyceride and cholesterol levels were lower with pioglitazone.

Deeg and colleagues[225] carried out a much larger comparison with 369 randomised to pioglitazone and 366 to rosiglitazone. The two drugs had differing effects on lipids, with rosiglitazone having the more atherogenic pattern, including higher LDL cholesterol levels.

Norris and colleagues[226] carried out a systematic review of the comparative effectiveness and safety of pioglitazone and rosiglitazone. They concluded effects of glycaemic control, weight and most adverse events were similar, but that rosiglitazone may increase total cholesterol compared to pioglitazone. However they concluded they had insufficient evidence with which to compare cardiovascular event rates.

Data from the Veterans Affairs trial have been used to assert that rosiglitazone does not cause cardiovascular harm by Duckworth and Moritz Veterans Affairs Diabetes Trial.[227] However this evidence seems dubious given that most patients in both arms were taking rosiglitazone.

The effect of all this has been that sales of rosiglitazone have fallen. A report on the newsletter, Endocrine Today,[228] states that sales fell from $617 million worldwide in the first quarter of 2007 to $327 million in the fourth quarter (though it does not say whether the price was reduced). A Canadian report notes that there was a sudden decline in the use of rosiglitazone after the publication of the Nissen meta-analysis, accompanied by an increase in the use of pioglitazone.[229]

5.3.1 Points raised in the consultation process.

In their responses to the draft guideline, Glaxo Smith Kline referred to new studies which provided safety data. The studies cited were the Action to Control Cardiovascular Risk in Diabetes Study.[230] and the VADT[227]

The ACCORD study was a trial of intensive versus standard therapy, aiming at a separation in HbA1c. The intensive group did worse with higher mortality, and no reduction in cardiovascular events. In the intensive group, 2.6% of patients died from cardiovascular causes, versus 1.8% in the standard group (p=0.02). 91% of the intensive group were treated with rosiglitazone versus 58% of the standard group. So ACCORD did not provide new data on the safety of rosiglitazone.

5.4 Summary

Little new has emerged since the last guideline was produced. Pioglitazone and rosiglitazone appear to have similar effectiveness in controlling hyperglycaemia, and similar toxicity in terms of oedema, heart failure and (in women only) fractures. However the current evidence suggests that rosiglitazone slightly increases cardiovascular mortality but that pioglitazone reduces it. Most of the regulatory and prescribing advisory bodies have asked for warnings on rosiglitazone but have allowed its continued use. Some have suggested that in future, pioglitazone be used in preference.

6 Chapter 6 Clinical effectiveness of pioglitazone in combination with insulin.

6.1 Objectives

In this chapter, we assess:

1. the effects of the combination of insulin treatment with pioglitazone compared to insulin treatment alone, and
2. the effects of the combination of insulin treatment with pioglitazone compared to pioglitazone treatment alone

6.2 Methods

6.2.1 Inclusion criteria

6.2.1.1 Types of studies

We considered randomised controlled trials with a minimum duration of 12 weeks, although trials of at least 24 weeks' duration were preferred.

6.2.2 Types of participants

Patients of any age and gender with type 2 diabetes.

6.2.3 Types of interventions

Pioglitazone in combination with any insulin regimen (including insulin plus metformin).

Comparisons could include:

a)

- long-acting insulin plus pioglitazone versus long-acting insulin alone
- long-acting insulin plus metformin plus pioglitazone versus long-acting insulin plus metformin
- twice daily mixture plus pioglitazone versus twice daily mixture
- twice daily mixture plus metformin plus pioglitazone versus twice daily mixture plus metformin

b)

- long-acting insulin plus pioglitazone versus pioglitazone alone
- long-acting insulin plus metformin plus pioglitazone versus pioglitazone plus metformin
- twice daily mixture plus pioglitazone versus pioglitazone alone
- twice daily mixture plus metformin plus pioglitazone versus pioglitazone plus metformin

There may be trials of the above with sulphonylurea as well as metformin.

6.2.4 Types of outcomes

We planned to consider the following outcome measures:

- HbA1c
- Frequency of hypoglycaemia, especially if severe

- Glycaemic excursions, including post-prandial hyperglycaemia
- Total daily dose of insulin
- Weight gain or loss
- Complication rates – retinopathy, nephropathy, myocardial infarction, angina, heart failure, stroke, amputation, death
- Adverse events
- Health-related quality of life

6.2.5 Search strategy

Relevant literature was identified, and comprehensiveness checked, by:

- Searches of bibliographic databases, Medline, Cochrane Library, and Embase
- Checking reference lists of retrieved studies
- Obtaining lists of published studies from manufacturers
- Our peer review process

Searches were also done to identify emerging evidence, from conference abstracts and trial registers. Studies available only in abstract were included in the assessment of clinical effectiveness if there is a paucity of studies published in full in peer reviewed journals, but they were reported with appropriate caution. Our default position is for studies available only in abstract not to be used.

Authors of previous studies were not contacted.

6.2.6 Quality assessment of studies

Randomised controlled trials were assessed on the following criteria based on the NICE guidelines manual:

- Method of randomisation
- Allocation concealed
- Participants and blinded
- Outcome assessors blinded
- Intention-to-treat analysis performed
- Proportion of participants excluded / lost to follow-up
- Power calculation
- Groups comparable at baseline

Again, overall quality of the trials was classified as good, moderate, or poor.

6.2.7 Data extraction

Data extraction was carried out by one researcher and a sample checked by another. Any disagreements were resolved through discussion, involving a third person if necessary.

6.2.8 Data analysis

The clinical effectiveness, relative to the key comparators, was assessed, in terms of difference in effect size.

Data were summarised in a meta-analysis and using tables and text. For dichotomous outcomes, odds ratios were calculated and a Mantel-Haenszel random effects model was used. For continuous outcomes, standardised mean differences were calculated and an

inverse variance random effects model was used. Heterogeneity was assessed using the chi-squared test.

6.3 Systematic Reviews

6.3.1 Search results

Eleven papers were identified as potentially relevant randomised controlled trials. Of these, eight fulfilled the inclusion criteria and compared pioglitazone plus insulin with insulin.[231-238] One compared pioglitazone plus insulin with pioglitazone. The remaining trials were excluded because they did not examine the comparison of interest and one was the uncontrolled extension of a trial that seemed relevant but could not be identified (see Table 23.)

Table 23: Excluded RCTs – insulin plus pioglitazone versus insulin

Study	Reason for exclusion
Davidson 2006 [239]	no insulin only group
Rosenblatt 2001 [240]	open-label extension without single treatment of a trial that could not be identified

6.3.2 Description of studies – insulin plus pioglitazone versus insulin

Characteristics of the included trials are shown in Appendix 6

Design. Seven trials were randomised double-blind placebo-controlled trials,[231 232,233,235-238] while one trial was a randomised open label trial.[234]The studies had different emphases: Asnani 2006 and Fernandez 2008 focussed on vascular reactivity; Berhanu 2007 focussed on reduction of insulin dosage; Mattoo 2005 focussed on glycaemic control, lipids and cardiovascular risk factors; Raz 2005 and Rosenstock 2002 focussed on glycaemic control; Scheen 2006 focussed on secondary prevention of macrovascular events; and Shah 2007 focussed on body fat distribution. Trial duration ranged between 12 and 36 weeks. Where stated, trials were sponsored by industry. Five trials were from the USA,[231 232,235,237,238] one included centres from a range of European countries,[236] and two included centres worldwide.[233,234]

Participants. The trials included between 20 and 1760 participants, with between 10 and 896 participants in each comparison group. The total number of patients assessed was 3092. All studies included participants with previous inadequate glucose control (with different definitions, not reported for Shah 2007). Inclusion criteria with respect to previous treatment varied substantially. Only five trials [232,233,235,237,238] required previous insulin treatment. Three trials [233,235,238] required previous insulin therapy with or without oral antidiabetic agents (where reported, previous insulin monotherapy ranged between 48 and 88%). The trial by Fernandez 2008 required previous insulin combination therapy,[232] and the trials by Shah 2007 included only insulin-treated obese patients.[237] Of the remaining trials, the trial by Berhanu 2007 [231] required previous combination therapy with or without insulin and in this trial, between 90 and 93% of patients had been on sulphonylurea plus metformin therapy without insulin. The study by Raz 2005 [234] required previous therapy with sulphonylurea (alone or as oral combination therapy) and over 80% of patients in that trial had been on sulphonylurea plus metformin previously. The study by Scheen 2006 [236] included patients previously on diet alone, oral agents, or insulin plus an oral agent and in that trial, over half the patients (53%) had been on sulphonylurea plus insulin, and the second largest group had been on sulphonylurea monotherapy (24%). Where reported, mean age of participants was between 46 to 59 years, the comparison groups included between 35 and 60% of women, mean BMI was between 29 and 37 kg/m2, and diabetes duration was between 6 and 14 years. The trial by Berhanu 2007 [231] included between 50 and 59% of Hispanic participants, and the study by Fernandez 2008 included only Mexican-American participants. [232]

Interventions. The trials used pioglitazone doses up to 45 mg/day. Four trials used titration schemes for pioglitazone (up to 45 mg/day, usually starting at 15 mg/day).[231,232,236,237] Three trials used fixed doses of 30 mg/day.[233 234,238] Rosenstock 2002 compared two pioglitazone doses, 15 and 30 mg/day.

As concerns the insulin therapy, Asnani 2006, Rosenstock 2002 and Scheen 2006 only specified that insulin therapy was continued as before. Rosenstock 2002 used a single blind insulin monotherapy lead-in period. Berhanu 2007 used a four week titration period for insulin (Humalog, Humulin 70/30 or Humulin N) and defined a target FPG of less than 140 mg/dL while avoiding hypoglycaemia. In the study by Fernandez 2008 patients could choose between multiple daily injections (basal-bolus therapy using combination of insulin glargine at bedtime plus premeal insulin aspart) or continuous subcutaneous infusions (basal infusion and premeal boluses of insulin aspart) and defined targets for blood glucose values (fasting and pre-meal capillary blood glucose 80 – 120 mg/dL, 2-h post-meal glucose <160 mg/dL, bedtime glucose <140 mg/dL). Mattoo 2005 used a three month insulin intensification period before randomisation; the insulin dose was reduced by 10% at randomisation to avoid hypoglycaemia and adjusted thereafter based on self-monitored blood glucose levels. Raz 2005 used biphasic insulin aspart 30/70. In the study by Scheen 2006, concomitant therapy with metformin was used by 47 to 52%, sulphonylurea alone by 16%, and metformin plus sulphonylurea by 10 to 11%. Shah 2007 did not give details of the insulin therapy.

Various studies specified co-interventions. Asnani 2006 allowed stable lipid lowering therapy with statins and anti-hypertensive therapy (including ACE inhibitors in all patients). In the study by Berhanu 2007 statins and metformin where continued as before. Fernandez 2008 changed all patients previously on ACE inhibitors or angiotensin II receptor blockers for blood pressure control to alpha-methyl dopa. Fernandez 2005 and Rosenstock 2002 allowed lipid lowering therapy as used before the study.

Outcomes. The trials used a variety of primary endpoints. HbA1c was the primary endpoint in the studies by Mattoo 2005, Raz 2005 and Rosenstock 2002. The primary endpoint in the study by Asnani 2006 was flow-mediated dilatation, in the study by Berhanu 2007 it was change in insulin dosage, Fernandez 2008 used vascular analyses as primary endpoint, the primary endpoint in the study by Scheen 2006 was a composite macrovascular endpoint, and in the study by Shah 2007 it was body fat distribution. All studies reported on end of study HbA1c values, six studies reported on hypoglycaemia,[231-236] one study reported on glycaemic excursions,[234] six studies reported on total daily dose,[231-236] six studies reported on weight change,[231-235,237] five studies reported on adverse events, six studies reported on lipid parameters,[231-235,238] while none of the studies reported on rates of diabetic secondary complications or health-related quality of life.

6.3.3 Quality of studies – insulin plus pioglitazone versus insulin

Details of the quality of included trials are shown in Table 24.

For four [231,233,234,238] of the eight trials, randomisation was adequate, while for the remaining four trials the randomisation procedure was not reported or unclear. Three trials [231,233,238] had adequate allocation concealment, while the rest of the trials did not report on allocation concealment. All but one trial [234] were described as double-blind. Five trials used intention-to-treat analysis.[231 233-236] Five trials reported on follow-up rates [231,233-235,238]and in those trials, between 77 and 92% of participants completed the trial, without any significant differences between comparison groups. Six of the eight trials reported that they had carried out a power calculation. [231 232,233,235,236,238] Two trials (reported as abstracts)[236 237]did not report relevant baseline characteristics, five trials reported that there comparison groups were similar at baseline, [232 233-235,238] while Berhanu 2007 stated that participants in the placebo group had a slightly higher BMI at baseline and longer diabetes duration, but it was unclear whether these differences were significant. All but one trial [237] reported on sources of funding and all funding included industry funding.

Table 24: Quality of included trials – insulin plus pioglitazone versus insulin

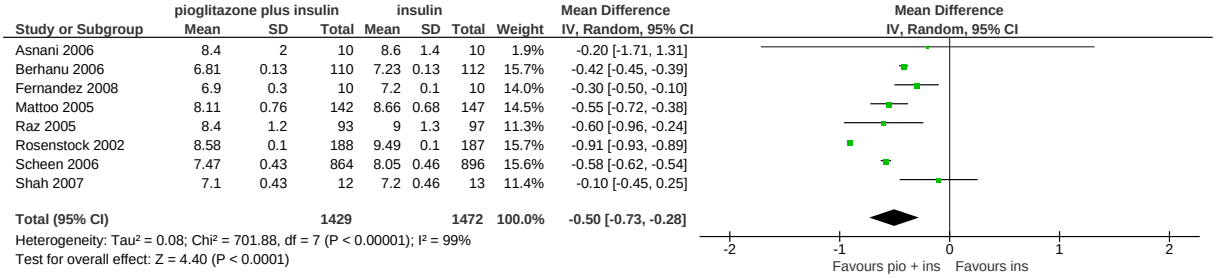
Study	Method of randomisation	Allocation concealment	Blinding	Intention to treat data analysis	Percentage who completed trial	Power calculation	Similarity of groups at baseline	Sponsorship/author affiliation
Asnani 2006 [238]	carried out by research pharmacist using predetermined randomisation code	yes	double-blind	not reported	**PIO + ins**: 80% **P + ins**: 80%	yes	yes	Takeda, NIH
Berhanu 2007 [231]	computer-generated schedule	yes	double-blind	yes	**PIO + ins**: 87.3% **P + ins**: 91.1%	yes	stated that placebo group had slightly higher BMI and longer diabetes duration, but no p-values given	Takeda Global R&D Centre
Fernandez 2008 [232]	not reported	not reported	double-blind	not reported	unclear – all?	yes (on vascular parameters)	yes	American Diabetes Association, Takeda Pharmaceuticals
Mattoo 2005 [233]	central randomisation table administered by an automated interactive voice system	yes	double-blind	yes	**PIO + ins**: 90% **P + ins**: 92%	yes	yes	Eli Lilly, Takeda Europe
Raz 2005 [234]	unclear ("assignment of lowest available patient number")	not reported	no	yes	**PIO + ins**: 78% **ins mono**: 77%	yes	yes	Novo Nordisk
Rosenstock 2002 [235]	not reported	not reported	double-blind	yes	**PIO15 + ins**: 84% **PIO30 + ins**: 91% **P + ins**: 88%	not reported	yes	Takeda Pharmaceuticals

Study	Method of randomisation	Allocation concealment	Blinding	Intention to treat data analysis	Percentage who completed trial	Power calculation	Similarity of groups at baseline	Sponsorship/author affiliation
Scheen 2006 [236]	central interactive voice-response system	not reported	double-blind	yes	not reported	yes	not reported	Takeda Europe, Eli Lilly
Shah 2007 [237]	not reported	not reported	double-blind	not reported	not reported	not reported – small numbers, probably underpowered	not reported	not reported

6.3.4 Results – insulin plus pioglitazone versus insulin

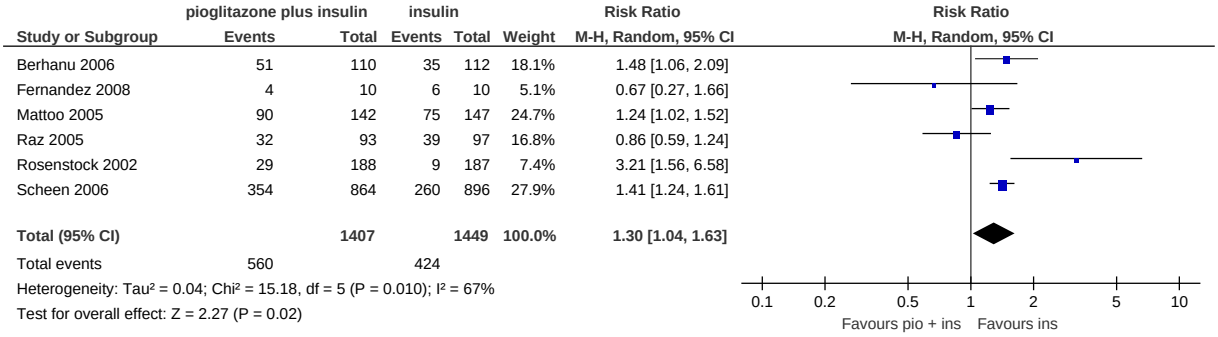
HbA1c. All studies reported HbA1c values and could be included in the meta-analysis. Baseline HbA1c values were between 7.6 and 10% in the pioglitazone plus insulin groups and between 7.8 and 9.8% in the insulin without pioglitazone groups. End-of-study HbA1c values were significantly lower in the groups taking pioglitazone plus insulin than in the groups taking insulin without pioglitazone (weighted mean difference -0.5%, 95% CI: -0.73, -0.28, p<0.0001). There was significant heterogeneity (p<0.00001). In the study by Mattoo 2005, 18% of patients on pioglitazone plus insulin and 6.9% of patients on insulin without pioglitazone attained HbA1c values of below 7.0%. There was no significant difference between patients using two or less and patients using three or more daily injections. Similarly, there was no significant difference between patients who had previously been on oral antidiabetic agents and those who had not been on oral agents. In the study by Rosenstock 2002, no significant difference in HbA1c was reported for the group using 15 mg/day of pioglitazone and the group using 30 mg/day.

Figure 11: Forest plot of HbA1c results – pioglitazone and insulin



Hypoglycaemia. Six studies reported on hypoglycaemia outcomes and could be summarised in a meta-analysis. There were significantly more patients with hypoglycaemic episodes in the pioglitazone plus insulin groups than with insulin without pioglitazone (relative risk 1.30, 95% CI: 1.04, 1.63, p=0.02). The results showed significant heterogeneity (p=0.01).

Figure 12: Forest plot of frequency of hypoglycaemia - pioglitazone and insulin



Dose. Six studies [231-236] reported insulin doses (as units per kg per day or as units per day). Only two studies reported standard deviations, so a meta-analysis could not be carried out reliably. Of the six studies, four found that the insulin plus pioglitazone groups used significantly less insulin than the insulin without pioglitazone groups (weighted mean difference -0.19 U/kg/day or -12.03 U/day). The remaining two studies did not report any p-values. Insulin dose ranged between 42 and 64 U/day or 0.5 to 1 U/kg/day in the pioglitazone groups and between 55 and 70 U/day or 0.7 to 1.2 U/kg/day in the groups taking no pioglitazone.

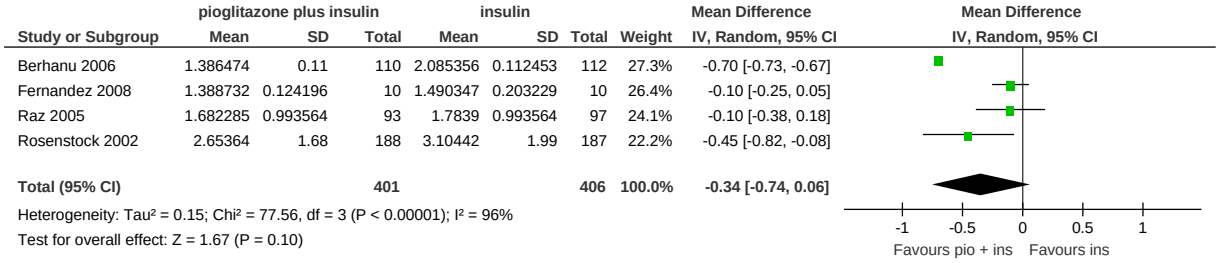
Weight change. Six studies reported weight change.[231-235,237] However, only one of the studies reported a measure of variability, so a meta-analysis could not be carried out reliably.

In most studies, patients in the insulin without pioglitazone groups gained less weight than patients in the insulin plus pioglitazone groups (mean difference 2.91 kg, range 3.85 to -3.50 kg), but no p-values were reported. Weight change ranged between +1.4 and +4.4 kg in the pioglitazone plus insulin groups and between 0.04 and +4.9 kg in the insulin only groups.

Lipid parameters. Four studies reported results for serum triglycerides and results could be summarised in a meta-analysis. [231,232,234,235]

Of the four studies, only two [231,235] found significantly reduced triglyceride values in the pioglitazone groups. Overall, the meta-analysis did not find any significant reduction in triglyceride levels with pioglitazone (weighted mean difference 0.34 mmol/L, 95% CI: -0.74, 0.06, p=NS). There was significant heterogeneity for all lipid parameters (triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol).

Figure 13: Forest plot of triglycerides (mmol/L) - pioglitazone and insulin



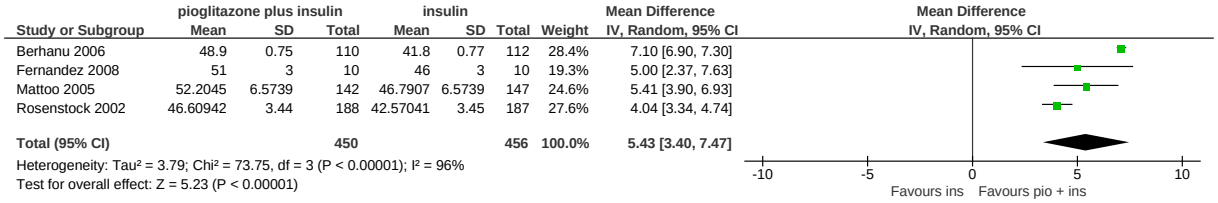
Four studies reported on total serum cholesterol.[231,232,234,235]

None of the studies found any significant difference in total cholesterol between the pioglitazone plus insulin and the insulin without pioglitazone groups.

Four studies reported on HDL-cholesterol, [231-233,235] all finding significantly increased values in the pioglitazone groups. Overall, HDL cholesterol was increased by a weighted mean difference of 5.43 mg/dL (95% CI: 3.40, 7.47, p<0.00001) in the pioglitazone groups.

HDL-cholesterol (mg/dL)

Figure 14: Forest plot of HDL cholesterol- pioglitazone and insulin



Four studies reported on LDL-cholesterol, [231-233,235] with none finding any significant difference between the pioglitazone plus insulin and the insulin without pioglitazone groups.

Adverse events. Where reported, there did not appear to be any significant difference in withdrawals due to adverse events between the pioglitazone plus insulin and the insulin without pioglitazone groups. The only adverse event (apart from weight gain) reported as occurring more frequently with pioglitazone was (peripheral) oedema, which was generally classified as mild to moderate, and which would be manageable with a diuretic. However, p-values were generally not reported.

Table 25: Results of included trials – insulin plus pioglitazone versus insulin

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
HbA1c					
Asnani 2006	HbA1c (%)	**PIO + ins**: 10.0 SD2.3% **P + ins**: 8.7 SD2.3%	**PIO + ins**: 8.4 SD2.0% **P + ins**: 8.6 SD1.4%		p not reported (p<0.05 for pio before and after)
Berhanu 2007	HbA1c (%)	**PIO + ins**: 8.4 SD0.13% **P + ins**: 8.6 SD0.13%	**PIO + ins**: 6.81% **P + ins**: 7.23%	**PIO + ins**: -1.6 SD0.11% **P + ins**: -1.4 SD0.11 %	p=NS
Fernandez 2008	HbA1c (%)	**PIO + ins**: 9.0 SD0.7% **P + ins**: 9.2 SD0.4%	**PIO + ins**: 6.9 SD0.3% **P + ins**: 7.2 SD0.1%		
Mattoo 2005	HbA1c (%)	**PIO + ins**: 8.85 SE0.11% **P + ins**: 8.79 SE0.1%	**PIO + ins**: 8.11 SE0.09% **P + ins**: 8.66 SE0.08%	difference between groups -0.55 SE0.1%	p<0.002
	percentage attaining HbA1c <7.0%		**PIO + ins**: 18% **P + ins**: 6.9%		
	HbA1c subgroups: patients using ≤2 or ≥3 insulin injections				no significant difference
	HbA1c subgroups: previous use of oral antidiabetic agents			previous use of oral agents: **PIO + ins**: -0.90 SE0.14% **P + ins**: -0.11 SE0.13% no previous use of oral agents: **PIO + ins**: -0.65 SE0.11% **P + ins**: -0.2 SE0.12%	no significant difference for subgroups
Raz 2005	HbA1c (%)	**PIO + ins**: 9.6 SD1.3%	**PIO + ins**: 8.4 SD1.2%		p=0.008

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
		ins mono: 9.5 SD1.3%	ins mono: 9.0 SD1.3%		
Rosenstock 2002	HbA1c (%)	**PIO15 + ins**: 9.75 SE0.1% **PIO30 + ins**: 9.84 SE0.1% **P + ins** : 9.75 SE0.1%		**PIO15 + ins**: -0.99 SE0.08% **PIO30 + ins** : -1.26 SE0.08% **P + ins** : -0.26 SE0.08%	p<0.01 pioglitazone versus placebo
Shah 2007	HbA1c (%)	**PIO + ins** : 7.6% **P + ins** : 7.8%	**PIO + ins** : 7.1% **P + ins** : 7.2%		p not reported, presumably non-significant
Scheen 2006	HbA1c (%)	**PIO + ins**: 8.4% **P + ins**: 8.5%	**PIO + ins**: 7.47% **P + ins**: 8.05%	**PIO + ins**: -0.93% **P + ins**: -0.45%	p<0.0001
hypoglycaemia					
Berhanu 2007	patients with hypoglycaemic events		**PIO + ins**: 46% (91% mild) **P + ins**: 31% (66% mild)		p<0.005
	severe hypoglycaemia (episodes)		**PIO + ins**: n=0 **P + ins**: n=4		p not reported
Fernandez 2008	patients with hypoglycaemic episodes		**PIO + ins**: n=4 **P + ins**: n=6		
Mattoo 2005	patients with subjective hypoglycaemic episodes		**PIO + ins**: 63.4% **P + ins**: 51.0%		p<0.05
	clinical hypoglycaemic episodes (blood glucose <2.8 mmol/L)				no significant difference

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
Raz 2005	major hypoglycaemic episodes		none		
	minor hypoglycaemic episodes (% patients)		**PIO + ins**: 12% **ins mono**: 15%		p not reported
	minor hypoglycaemic episodes (episodes)		**PIO + ins**: 15 **ins mono**: 47		p not reported
	symptoms only (% patients)		**PIO + ins**: 34% **ins mono**: 40%		p not reported
	symptoms only (episodes)		**PIO + ins**: 115 **ins mono**: 171		p not reported
	incidence (per patient-week for all episodes)		**PIO + ins**: 0.083 **ins mono**: 0.132		p<0.05
	nocturnal hypoglycaemia (episodes)		**PIO + ins**: 0 **ins mono**: 8		p not reported
Rosenstock 2002	hypoglycaemia		**PIO15 + ins**: 8% **PIO30 + ins**: 15% **P + ins**: 5% (all considered mild to moderate)		
Scheen 2006	hypoglycaemia (not specified further)		**PIO + ins**: 41% **P + ins**: 29%		p<0.0001
glycaemic excursions					
Raz 2005					measurements before dinner, 90 mins after dinner, and at bedtime significantly lower in PIO + ins group than in ins monotherapy group
total daily dose					
Berhanu 2007	daily insulin dose	**PIO + ins**: 55.8 SD2.95		**PIO + ins**: -12.0 SD1.84 units **P + ins**: +0.8 SD1.84 units	p<0.001

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
		units **P + ins**: 57.7 SD2.95 units		adjusted mean difference between groups -12.5 units (95% CI: -17.5, -8.0)	
Fernandez 2008	daily insulin dose	all groups: ~1.2 U/kg/day	**PIO + ins**: 1.0 U/kg/day **P + ins**: ~1.2 U/kg/day		p not reported
Mattoo 2005	daily insulin dose	**PIO + ins**: 0.96 SE0.03 U/kg/day **P + ins**: 0.92 SE0.03 U/kg/day	**PIO + ins**: 0.76 SE0.02 U/kg/day **P + ins**: 0.94 SE0.02 U/kg/day	difference between groups -0.18 SE0.02 U/kg/day	p<0.002
Raz 2005	daily insulin dose	**PIO + ins**: 0.2 U/kg/day **ins mono**: 0.3 U/kg/day	**PIO + ins**: 0.5 U/kg/day **ins mono**: 0.7 U/kg/day	**PIO + ins**: +0.3 U/kg/day **ins mono**: +0.4 U/kg/day	p=0.002
Rosenstock 2002	daily insulin dose	**PIO15 + ins**: 70.2 SE34.0 U/day **PIO30 + ins**: 72.3 SE38.5 U/day **P + ins** : 70.7 SE33.5 U/day	**PIO15 + ins**: 67.3 SE33.5 U/day **PIO30 + ins**: 64.2 SE32.7 U/day **P + ins** : 70.1 SE33.9 U/day		p not reported
Scheen 2006	daily insulin dose	**PIO + ins**: 47 U/day **P + ins**: 47 U/day	**PIO + ins**: 42 U/day **P + ins**: 55 U/day		p<0.0001; at final visit, insulin discontinued in 9% of pioglitazone group and 2% of placebo group (p<0.0001)
weight change					
Berhanu 2007	weight (kg)			**PIO + ins**: +4.39 kg **P + ins**: +2.42 kg	p not reported
	patients reporting weight gain			**PIO + ins**: n=10	p not reported

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
				P + ins: n=3	
Fernandez 2008	weight (kg)			**PIO + ins**: +4.4 kg **P + ins**: +1.7 kg	p not reported
Mattoo 2005	weight (kg)			**PIO + ins**: +4.05 SE4.03 kg **P + ins**: +0.20 SE2.92 kg	p not reported
Raz 2005	weight (kg)			**PIO + ins**: +4.0 kg **ins mono**: +2.2 kg	p not reported
	patients experiencing weight gain (%)			**PIO + ins**: 8% **ins mono**: 2%	p not reported
Rosenstock 2002	weight (kg)	**PIO15 + ins**: 95.4 SE17.6 kg **PIO30 + ins**: 98.7 SE17.7 kg **P + ins** : 95.4 SE17.0 kg		**PIO15 + ins**: +2.3 kg **PIO30 + ins**: +3.7 kg **P + ins** : -0.04 kg	p not reported; weight gain related to decreases in HbA1c, p=0.002
Shah 2007	weight (kg)	**PIO + ins**: 107.1 kg **P + ins**: 108.7 kg	**PIO + ins**: 112.0 kg **P + ins**: 110.1 kg		p not reported, presumably non-significant
complication rates					
Berhanu 2007	cardiac events			**PIO + ins**: 5.5% **P + ins**: 10.7% (mostly ECG abnormalities)	p not reported
	deaths			no deaths	
lipid parameters					
Berhanu 2007	total cholesterol (mg/dL)	**PIO + ins** : 178 SD3.53 mg/dL **P + ins** : 183 SD3.6 mg/dL		**PIO + ins**: +5.7 SD2.75 mg/dL **P + ins**: +4.7 SD2.78 mg/dL	p=NS

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
	HDL cholesterol (mg/dL)	**PIO + ins** : 44.6 SD1.3 mg/dL **P + ins** : 42 SD1.3 mg/dL		**PIO + ins**: +4.3 SD0.75 mg/dL **P + ins**: -0.2 SD0.77 mg/dL	p<0.001
	LDL cholesterol (mg/dL)	**PIO + ins** : 107 SD3.1 mg/dL **P + ins** : 111 SD3.2 mg/dL		**PIO + ins**: +4.0 SD2.37 mg/dL **P + ins**: +0.9 SD2.37 mg/dL	p=NS
	triglycerides (mg/dL)	**PIO + ins** : 123 SD7.5 mg/dL **P + ins** : 141 SD7.6 mg/dL		**PIO + ins**: -0.2 SD9.80 mg/dL **P + ins**: +43.7 SD9.96 mg/dL	p<0.001
Fernandez 2008	total cholesterol (mg/dL)	**PIO + ins** : 176 SD9 mg/dL **P + ins** : 195 SD9 mg/dL	**PIO + ins** : 175 SD16 mg/dL **P + ins** : 180 SD8 mg/dL		p=NS
	LDL cholesterol (mg/dL)	**PIO + ins**: 107 SD5 mg/dL **P + ins**: 121 SD8 mg/dL	**PIO + ins**: 105 SD12 mg/dL **P + ins**: 115 SD7 mg/dL		p=NS
	HDL cholesterol (mg/dL)	**PIO + ins**: 45 SD3 mg/dL **P + ins**: 49 SD4 mg/dL	**PIO + ins**: 51 SD3 mg/dL **P + ins**: 46 SD3 mg/dL		p<0.05 pioglitazone versus baseline
	VLDL cholesterol (mg/dL)	**PIO + ins**: 109 SD16 mg/dL **P + ins**: 113 SD24 mg/dL	**PIO + ins**: 88 SD15 mg/dL **P + ins**: 93 SD19 mg/dL		
	triglycerides (mg/dL)	**PIO + ins**: 148 SD17 mg/dL	**PIO + ins**: 123 SD11 mg/dL		p<0.05 pioglitazone versus baseline

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
		P + ins: 146 SD15 mg/dL	**P + ins**: 132 SD18 mg/dL		
Mattoo 2005	HDL cholesterol (mmol/L)	**PIO + ins** : 1.23 SE0.03 mmol/L **P + ins** : 1.24 SE0.03 mmol/L	**PIO + ins** : 1.35 SE0.02 mmol/L **P + ins** : 1.21 SE0.02 mmol/L	difference between groups 0.13 SE0.03 mmol/L	p<0.002
	LDL cholesterol (mmol/L)	**PIO + ins** : 3.20 SE0.09 mmol/L **P + ins** : 3.18 SE0.08 mmol/L	**PIO + ins** : 3.18 SE0.06 mmol/L **P + ins** : 3.10 SE0.06 mmol/L		p=NS
Raz 2005	triglycerides (mg/dL)		**PIO + ins**: 149 SD88 mg/dL **ins mono**: 158 SD88 mg/dL		p=NS
	total cholesterol (mg/dL)		**PIO + ins**: 212 mg/dL **ins mono**: 204 mg/dL		p=NS
	HDL cholesterol (mg/L)			difference between PIO + ins versus ins mono +4 SD1 mg/dL	p<0.01
	LDL cholesterol (mg/L)			no data shown	p=NS
Rosenstock 2002	triglycerides (mmol/L)	**PIO15 + ins** : 2.61 SE0.2 mmol/L **PIO30 + ins** : 2.96 SE0.2 mmol/L **P + ins** : 2.74 SE0.2 mmol/L		**PIO15 + ins** : +5.35 SE6.56% **PIO30 + ins** : -10.35 SE6.54% **P + ins** : +13.30 SE6.63%	p<0.05 PIO30 versus placebo

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
	HDL cholesterol (mg/dL)	**PIO15 + ins** : 43.42 SE0.95 mg/dL **PIO30 + ins** : 42.71 SE0.94 mg/dL **P + ins** : 42.66 SE0.96 mg/dL		**PIO15 + ins** : +7.07 SE1.58% **PIO30 + ins** : +9.13 SE1.57% **P + ins** : -0.21 SE1.59%	p<0.05 PIO30 versus placebo
	total cholesterol (mg/dL)	**PIO15 + ins** : 213.08 SE3.57 mg/dL **PIO30 + ins** : 207.32 SE3.53mg/dL **P + ins** : 214.03 SE3.58 mg/dL		**PIO15 + ins** : +1.40 SE1.06% **PIO30 + ins** : +0.40 SE1.05% **P + ins** : -0.66 SE1.07%	p=NS
	LDL cholesterol (mg/dL)	**PIO15 + ins** : 127.33 SE3.07 mg/dL **PIO30 + ins** : 121.69 SE3.06mg/dL **P + ins :** 130.95 SE3.05 mg/dL		**PIO15 + ins**: +2.83 SE1.80% **PIO30 + ins**: +5.05 SE1.71% **P + ins** : -1.41 SE1.74%	p=NS
adverse events					
Berhanu 2007	oedema			**PIO + ins**: n=10 **P + ins**: n=5 (all mild to moderate)	p not reported
	serious adverse events			**PIO + ins**: n=4 **P + ins**: n=2 (none considered to be related to study medication)	p not reported

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
Mattoo 2005	withdrawal due to adverse events			**PIO + ins**: n=7 **P + ins**: n=3	p not reported
	oedema			**PIO + ins**: n=20 (10 classified as mild) **P + ins**: n=5 (3 classified as mild)	p not reported
Raz 2005	withdrawal due to adverse events			**PIO + ins**: n=1 **ins mono**: n=2	p not reported
	patients with product-related adverse events			**PIO + ins**: 28% **ins mono**: 20%	p not reported
	peripheral oedema			**PIO + ins**: 6% **ins mono**: 0	p not reported
	serious adverse events			**PIO + ins**: n=0 **ins mono**: n=2 (none considered to be related to study medication)	
Rosenstock 2002	withdrawal due to adverse events			**PIO15 + ins**: 1.6% **PIO30 + ins**: 2.6% **P + ins** : 3.2%	p not reported
	oedema			**PIO15 + ins**: 12.6% **PIO30 + ins**: 17.6% **P + ins** : 7.0%	p not reported
	cardiovascular adverse events			**PIO15 + ins and PIO30 + ins**: 7.9% **P + ins** : 7.0%	p=NS; none considered related to study medication
Scheen 2006	oedema			**PIO + ins**: 31% **P + ins**: 18%	p<0.0001
HR QoL not reported					

6.3.5 Description of studies – insulin plus pioglitazone versus pioglitazone

There was only one trial, published as an abstract, comparing pioglitazone with pioglitazone plus insulin. Characteristics of the included trial are shown in Appendix 7

The focus of the study by Raskin 2006 [241,242] was on the safety and efficacy of BIAsp 30 (30% soluble and 70% protaminated insulin aspart) in insulin-naïve type 2 diabetes patients taking any two oral antidiabetic agents. The study was a randomised parallel group trial with a duration of 34 weeks and was carried out in the USA.

Participants. The trial included 181 participants (93 and 88 in each comparison group). The trial included insulin-naïve type 2 diabetes patients with a HbA1c value between 7.5 and 12% taking any two oral antidiabetic agents. No demographic characteristics were reported.

Interventions. The trial compared optimised treatment with a combination of pioglitazone and metformin with BIAsp 30 added to an optimised treatment with combination of pioglitazone and metformin. BIAsp 30 was initialised at 6 U twice a day (prebreakfast and presupper) and titrated to target blood glucose values of 4.4 to 6.1 mmol/L by an algorithm-directed forced titration. There was an eight week run-in phase during which treatment was changed to metformin (2500 mg/day) and pioglitazone (30 or 45 mg/day).

Outcomes. The primary endpoint was not reported (but was presumably HbA1c). Apart from HbA1c, minor hypoglycaemia (blood glucose <3.1 mmol/L) and weight were reported.

Quality. The abstract gave no information on the method of randomisation, allocation concealment, blinding, intention-to-treat analysis, the percentage of participants who completed the trial, whether a power calculation was carried out, or whether the comparison groups were comparable at baseline. Funding was by Novo Nordisk.

6.3.6 Results – insulin plus pioglitazone versus pioglitazone

The trial by Raskin 2006 found a significantly greater reduction of HbA1c at study end in the BIAsp 30 plus metformin plus pioglitazone group than in the metformin plus pioglitazone group (-1.5% versus -0.2%, $p<0.0001$). There were also larger proportions of patients reaching HbA1c values less than 7% in the BIAsp 30 plus metformin plus pioglitazone group (76.3% versus 24.1% in the metformin plus pioglitazone group), as well as values less than or equal to 6.5% (59.1 versus 11.5%), values less than or equal to 6% (33.3 versus 2.3%) and values less than or equal to 5.5% (14.0 versus 0%). However, the BIAsp 30 plus metformin plus pioglitazone group had significantly more minor hypoglycaemic events than the metformin plus pioglitazone group (8.3 versus 0.1 events/year, $p<0.001$). The patients in the BIAsp 30 plus metformin plus pioglitazone group also gained significantly more weight than the patients in the metformin plus pioglitazone group (4.6 versus 0.8 kg, $p<0.05$). Peripheral oedema occurred in 10% of patients in the BIAsp 30 plus metformin plus pioglitazone group and in 12% of patients in the metformin plus pioglitazone group.

Table 26: Results of included trials – pioglitazone plus insulin versus pioglitazone

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
HbA1c					
Raskin 2006	HbA1c (%)	**BIAsp 30 + met + pio**: 8.1 SD1.0% **met + pio**: 7.9 SD0.9%	**BIAsp 30 + met + pio**: 6.5 SD1.0% **met + pio**: 7.8 SD1.2%	**BIAsp 30 + met + pio**: -1.5% **met + pio**: -0.2%	p<0.0001
	% with HbA1c <7.0%		**BIAsp 30 + met + pio**: 76.3% **met + pio**: 24.1%		p not reported
	% with HbA1c ≤6.5%		**BIAsp 30 + met + pio**: 59.1% **met + pio**: 11.5%		p not reported
	% with HbA1c ≤6.0%		**BIAsp 30 + met + pio**: 33.3% **met + pio**: 2.3%		p not reported
	% with HbA1c ≤5.5%		**BIAsp 30 + met + pio**: 14.0% **met + pio**: 0%		p not reported
hypoglycaemia					
Raskin 2006	minor hypoglycaemia (events/year)		**BIAsp 30 + met + pio**: 8.3 events/year **met + pio**: 0.1 events/year		p<0.001
weight					
Raskin 2006				**BIAsp 30 + met + pio**: +4.6 SD4.3 kg **met + pio**: +0.8 SD3.2 kg	p<0.05
adverse events					
Raskin 2006	peripheral oedema		**BIAsp 30 + met + pio**: 10% **met + pio**: 12%		

6.4 Discussion

Summary. Eight randomised controlled trials were identified comparing combinations of insulin and pioglitazone with insulin without pioglitazone regimes (two published as abstracts only). One trial (published as abstract only) was identified comparing a pioglitazone plus insulin regime with a pioglitazone without insulin regime. Compared to the insulin regimes, the pioglitazone plus insulin regimes reduced HbA1c by a mean of -0.5% (95% CI: -0.73, 0.28, p<0.0001). However, hypoglycaemic events were increased with the pioglitazone regimes (relative risk 1.30, 95% CI: 1.04, 1.63, p=0.02). Where reported, studies tended to find reduced insulin doses in the pioglitazone groups, as well as increased HDL-cholesterol values. None of the other lipid parameters reported (triglycerides, total cholesterol, LDL-cholesterol) showed any systematic differences between the comparison groups. The studies tended to show increased weight (mean difference 2.91 kg) and more peripheral oedema with pioglitazone. The one trial comparing a pioglitazone plus insulin (plus metformin) with a pioglitazone (plus metformin) regime found significantly lower HbA1c values in the groups taking insulin but also more minor hypoglycaemic events and more weight gain. The rates of peripheral oedema appeared to have been similar between the groups.

7 Chapter 7: Literature review of economic studies on new drugs for diabetes

7.1 Methods

7.1.1 Search strategy

The databases Medline, Embase, Science Citation Index, ISI Proceedings and NHS-EED were searched, as described in Appendix 1b. Articles for inclusion were retrieved and initially screened by one author, and then further screened selected by the health economist for inclusion.

7.2 GLP-1: Exenatide

7.2.1 Quality of Life studies

Secnik and colleagues[67] summarised the quality of life effect of exenatide 10µg twice daily and glargine once daily as observed in a 26 weeks phase III trial among 455 per-protocol patients with type 2 diabetes. These were added to patients' existing regimes of metformin and a sulfonylurea. Both the addition of exenatide and the additional of glargine demonstrated statistically significant improvements in the SF-36 vitality subscale score: from 53.18 to 56.30 for exenatide and from 55.18 to 57.62 for glargine. They were also associated with statistically significant improvements in the Diabetes Symptom Checklist-Revisited (DSC-R) (range 0-5) total score: with exenatide recording an improvement from 1.07 to 0.90, and glargine an improvement from 0.99 to 0.84. Both exenatide and glargine were reported as showing statistically significant improvements in the psychology: fatigue, psychology: cognitive, ophthalmology, hypoglycaemia and hyperglycaemia subscales of the DSC-R. Statistically significant improvements in the Diabetes Treatment Satisfaction Questionnaire were also observed: from 26.41 to 29.48 for exenatide and from 26.31 to 30.04 for glargine, with the perceived frequency of both hypoglycaemia and hyperglycaemia recording improvements for both groups. However, while the change in EQ-5D was of similar size between the two groups, for exenatide the change from 0.82 to 0.85 was not statistically significant with p=0.08 while for glargine the change from 0.84 to 0.87 was with p=0.05.

A study by Yurgin and colleagues[68], available as an abstract only, reported the effects of exenatide as compared to biphasic insulin when added to existing regimes of metformin and a sulfonylurea from a 52 week non-inferiority trial among 505 patients with type 2 diabetes. The HbA1c effects were similar, -0.98% for exenatide and -0.88% for biphasic insulin. Exenatide led to statistically significant improvements in EQ-5D VAS scale of 3.39, the SF-36 vitality scale of 3.89 and the DSC-R of -0.13. No significant effect was observed in the treatment flexibility scale. There were no statistically significant changes in these for biphasic insulin, though it should be noted the there was also no statistically significant difference between exenatide and biphasic insulin with the exception of the DSC-R which recorded an increase under biphasic insulin of +0.05.

7.2.2 Weight, Nausea, Quality of Life and Cost of Treatment

Ratner and colleagues[243] reported a progressive reduction in weight of an average around 2.4kg by week 30 within a placebo controlled trial of exenatide among 150 patients with type 2 diabetes. From these, 92 patients also completed a 52 week follow-up study to give a total time horizon of 82 weeks. The average weight loss at 30 weeks was -3.0kg, this increasing to -5.3kg by week 82.

Blonde and colleagues[244] report similar results from a somewhat larger placebo controlled trial in 1,446 patients, of whom 1,125 or 78% completed the initial 30 week trial. 974 of these patients entered the open label phase, 668 of these having been originally randomised to receive exenatide within the placebo controlled trial. Only 551 of these patients could be evaluated at the 82 week point due to enrolment dates, 314 of these completing the 52 week follow-up study. The ITT group and the completer cohort had similar weights and BMIs: 98kg and 34kg/m2 and 99kg and 34kg/m2 respectively. For this 82 week completer cohort, the average change at 30 weeks was -2.1kg, which was reportedly similar to the range of -1.6kg to -2.8kg reported for the 10µg arm of the placebo controlled trial. Unfortunately the mean change for the 10µg arm was not stated, and it should also be noted that the placebo control group also experience weight loss of between -0.3kg and -0.6kg at week 30. Among the 82 week completer cohort at week 82 the average weight loss was 4.4kg, with 81% of patients having lost weight. The average change in weight among the 82 week completer cohort showed a generally increasing trend with BMI: for patients of less than 25kg/m2 the average weight loss was 2.9%, while for patients in increasing BMI increments of 5kg/m2 the average weight loss was 3.6%, 4.6%, 4.3% until for those with a BMI of more than 40kg/m2 the average weight loss was 5.5%.

As summarised within the clinical effectiveness section, for the direct comparison with glargine, Heine and colleagues[53] reported among a patient population with an average BMI of 31kg an average 2.3kg weight loss among those starting exenatide by week 26, as compared to an average weight gain of 1.8kg for those starting glargine.

The submission for exenatide to the Scottish Medicines Consortium, citing trial results for exenatide in terms of weight loss, reported an additional utility estimation exercise conducted among 129 diabetics. This used standard gamble to estimate the utility for patients in their current health state, a basic representative health state for patients with type 2 diabetes, and for the representative health state plus a variety of combinations of nausea and weight loss. The average utility for patients' current health state and the notional representative health state was 0.891 and 0.873: a difference of -0.018. The absolute utility impacts of nausea and weight change were estimated as shown in Table 27.

Table 27: Utility values for nausea and weight change

Nausea not experienced	**Weight change**	**Utility change**
	+5%	-0.065
	+3%	-0.044
	-3%	+0.020
	-5%	+0.032
Nausea experienced	**Weight change**	**Utility change**
	+5%	-0.095
	+3%	-0.073
	Nil	-0.043
	-3%	-0.028
	-5%	-0.010

Dennett and colleagues,[245] in a study funded by Eli Lilly, conducted a systematic review of the literature to evaluate the impact of weight gain on patients with or without type 2 diabetes. Utility scores for patients without diabetes who were of normal weight were between 0.71 and 0.93, while for obese patients without diabetes the scores ranged from 0.60 to 0.91. Utility scores were lower for patients with diabetes, ranging from 0.57 to 0.77 for those of normal weight as compared to 0.33 to 0.70 for those that were obese. The authors concluded that older studies tended to examine changes in weight or BMI without controlling for whether weight was being gained or lost. More recent studies suggest that changes may be asymmetrical, with a percentage gain in weight or BMI having a lesser effect than the

same percentage loss. However, no particular study, method of elicitation or values were arrived at or recommended for use. Within the summary of results presented by Dennett and colleagues it is also not clear to what extent other comorbities have been controlled for within the estimates. Bagust and Beale,[246] as referenced within the Dennet and colleagues review, did control for other comorbidities and found that through time trade off estimates that for every BMI point above 25kg/m2 utility declined by 0.0061. Coffey and colleagues,[247] also having controlled for comorbidities, found that being obese with a BMI of more than 30kg/m2 reduced utility by 0.021.

Yu and colleagues[129], in a study funded by Eli Lilly and Amylin Pharmaceuticals, analysed data from US Health Maintenance Organisations to assess the impact upon overall treatment costs of weight changes among 458 patients with type 2 diabetes. Over the six months of weight measurement, around half of patients gained weight while half were described as non-weight gainers, both groups having a similar average BMI at baseline of around 34kg/m2. In the year subsequent to the change in weight, emergency room visits were similar between the groups at 11.6% for the weight gainers as compared to 11.1% for the non-weight gainers. Hospitalisations were higher among weight gainers at 8.0% as compared to 4.7%, though this was not statistically significant with p=0.143.Total healthcare costs were statistically significantly different, being US$3,167 for the weight gainers as compared to US$1,852 with p=0.003.

Regression analyses appeared to suggest about a 3% to 4% change in costs for every 1% change in weight. Within an additional regression analysis that controlled for patient obesity, percentage point weight losses among the non-obese were not associated with cost savings but reduced costs among the obese by 6%. Within this analysis for both the non-obese and the obese, percentage point increases in weight increase costs by between 2% and 3%, but these estimates for the sub-groups were not statistically significant. These results illustrate the impact of obesity upon the overall treatment costs of diabetes, but cannot be directly appended to the modelling of exenatide given that the effects of obesity on complications and costs will be being indirectly modelled through the effect upon systolic blood pressure and high density lipids as a ratio of total lipids.

Cost effectiveness studies

Edwards and colleagues[248] undertook a systematic literature review of the clinical effects of exenatide as compared to glargine and NPH insulin, all these being additional to a regime of metformin and sulfonylurea therapy. Only one paper met their inclusion criteria: the 24 week Riddle and colleagues study.[169] Based upon this, they performed a simple cost effectiveness analysis, anticipating that for every US$100 spent the reduction in HbA1c would be 0.091, 0.655 and 0.201 for exenatide, glargine and NPH respectively. Similarly, they anticipated that for every US$100 spent there would be a 0.19 kg weight loss for exenatide. Both forms of insulin were associated with weight gain. But given the outcome measures of the analysis and that exenatide was more expensive than either of the insulin treatments, few conclusions as to the treatments' relative cost effectiveness can be drawn.

Shaya and colleagues[249] analysed manufacturer data for 5µg and10µg exenatide to evaluate the cost effectiveness of exenatide relative to placebo using the CORE cost effectiveness model. Unfortunately, no details of the inputs and assumptions used for the modeling were provided within the paper, but the manufacturer summary referenced suggested the following clinical inputs at 30 weeks, as shown in Table 28:

Table 28: HbA1c and weight changes as used by Shaya and colleagues

	placebo			exenatide 5 µg			exenatide 10 µg		
	n	HbA1c	Weight	n	HbA1c	Weight	n	HbA1c	Weight
With sulfonylurea	123	+0.1%	-0.6kg	125	-0.5%	-0.9kg	129	-0.9%	-1.6kg
With metformin	113	+0.1%	-0.3kg	110	-0.4%	-1.6kg	113	-0.8%	-2.8kg
With met+sulf	247	+0.2%	-0.9kg	245	-0.6%	-1.6kg	241	-0.8%	-1.6kg

This modelling yielded cost effectiveness estimates of US$43,814 per additional life year and US$48,921 per QALY. Curtailing the time horizon to 20 years has limited impact upon modelled outputs, but curtailing the time horizon to only 5 years increases the cost per life year to US$359,757 and the cost per QALY to US$104,697. As would be anticipated, the effect upon the cost per life year is somewhat larger as relatively few in either arm will have died at the 5 year point, but the increase in the cost per QALY underlines the importance of extrapolation and longer terms complications within the lifetime estimate of cost effectiveness. The assumptions made in terms of longer term effects upon HbA1c and weight were not stated, and the likelihood of transferring to an insulin regime at some point for both the placebo arm and the exenatide arm was similarly not made clear.

Minshall and colleagues[250] in assessing the cost effectiveness of exenatide relative to placebo, appear to have used similar 30 week clinical effectiveness data from placebo controlled trials as Shaya and colleagues, though in more disaggregate form as outlined in Table 29:

Table 29: HbA1c and weight changes as used by Minshall and colleagues

		placebo		exenatide 5 µg		exenatide 10 µg	
All patients	**n**	**HbA1c**	**Weight**	**HbA1c**	**Weight**	**HbA1c**	**Weight**
With sulfonylurea	377	+0.1%	-0.6kg	-0.5%	-0.9kg	-0.9%	-1.6kg
With metformin	336	+0.1%	-0.3kg	-0.4%	-1.6kg	-0.8%	-2.8kg
With met+sulf	733	+0.2%	-0.9kg	-0.6%	-1.6kg	-0.8%	-1.6kg
For patients with HbA1c <9%							
With sulfonylurea	239	+0.1%	..	-0.4%	..	-0.7%	..
With met+sulf	513	+0.3%	..	-0.4%	..	-0.5%	..
For patients with HbA1c ≥9%							
With sulfonylurea	138	+0.1%	..	-0.6%	..	-1.2%	..
With met+sulf	220	+0.0%	..	-0.9%	..	-1.4%	..
For patients with BMI <30							
With metformin	89	..	+0.4kg	..	-0.5kg	..	-2.4kg
For patients with BMI ≥30							
With metformin	247	..	-0.5kg	..	-2.1kg	..	-3.0kg

This 30 week data was augmented with 82 week clinical effectiveness estimates from an optional open label extension study within which exenatide patients had a reported sustained HbA1c reduction of -1.1% and a progressive mean body weight reduction of 4.4kg. The 82 week data was also used to estimate a reduction in systolic blood pressure of -1.3mmHg, a reduction in LDL cholesterol of -1.6mg/dL, and increase in HDL cholesterol of +4.6mg/dL and a reduction in triglycerides of 39mg/dL. After the 82 weeks point the trend in these variables was assumed to follow identified UKPDS trend, as seems likely to have been assumed for the placebo arm subsequent to the 30 week point. Medicare costs were applied to adverse events, with utilities being drawn from the European CODE-2 study EQ-5D values as reported in Bagust & Beale.[246] As with Shaya and colleagues,[249] the paper used the CORE model to assess the cost effectiveness of adding exenatide to metformin and sulfonylurea as compared to patients remaining on just metformin and sulfonylurea. Despite a presumably

worsening HbA1c over time in both arms, there does not appear to have been any consideration of patients transferring to insulin therapy.

Results for exenatide among patients of average age 56, 7 years duration of diabetes and a baseline of 8.3% HbA1c, 123mmHg systolic blood pressure, a BMI of 34, HDL of 38mg/dL, LDL of 115mg/dL and triglycerides of 239mg/dL over a 30 years time horizon, were a discounted life expectancy of 9.63 years and a quality adjusted life expectancy of 6.33, coupled with a lifetime cost of US$86,281. For the placebo arm the parallel estimates were 9.10 life years, 5.81 QALYs and a cost of US$67,531, yielding a net impact from exenatide of 0.53 life year, 0.52 QALYs and US$18,750 to yield a cost effectiveness estimate of US$36,133 per QALY. Shortening the time horizon to 20 years had limited impact upon cost effectiveness, though a time horizon of only 10 years worsened the anticipated cost effectiveness to US$64,538 per QALY.

A 20% lessening of the impact of exenatide on HbA1c from -1.1% to -0.88% had roughly proportionate impact upon cost effectiveness, worsening it by 16% to US$41,917 per QALY. Removing the impact upon weight and systolic blood pressure had reportedly little impact upon cost effectiveness, though values were not given. Removing the lipid effects also worsened the cost effectiveness by around 16% to US$41,738 per QALY. Subgroup analyses among those with HbA1c<9% at baseline and those with HbA1c ≥9% suggested marked differences in cost effectiveness, US$45,971 per QALY and US$20,548 per QALY respectively.

The relevance of the studies of both Shaya and colleagues[249] and Minshall and colleagues[250] are limited in that there appears to be no consideration of patients transferring to insulin therapy as HbA1c worsens. Ray and colleagues[251] in part addressed this, also having used the CORE model but to model the cost effectiveness of exenatide relative to glargine. Exenatide was anticipated to result in a slightly lower improvement in HbA1c than glargine, but greater improvements in a number of other outcomes with the central values as shown in Table 30, where nausea was the proportion of patients experiencing nausea, and hypoglycaemia was the average number of hypoglycaemic events per year.

Table 30: Outcomes changes used by Ray and colleagues

	HbA1c	SBP	Cholestrol	LDL	HDL	Triglyc.	BMI	Nausea	Hypogl.
exenatide	-0.99%	-4.15	-3.47	-1.54	+1.54	-15.04	-0.80	57.1%	6.94
glargine	-1.07%	-0.57	-0.39	+5.80	+1.54	-30.08	+0.55	8.6%	5.84

The base case cost of exenatide was drawn from the US cost converted at the prevailing exchange rate, as the UK wholesale cost for exenatide had not been formalised. The insulin dose was assumed to be 25IU in the first year, and thereafter 40IU. Annual blood glucose monitoring costs were assumed to be £290 in the exenatide arm and £414 in the glargine arm, based upon predictions from a UK survey of healthcare professionals and patients. Prices of complications were drawn from UK sources and indexed to 2004 prices, while utility values were mainly drawn from UKPDS data as reported in Clarke and colleagues.[252] Utility gains from weight loss were also applied to the first two years of the simulations, the values for this being taken from CODE-2 data that jointly analysed the effect of nausea and BMI. Subsequent to the two year point the CODE-2 time trade-off data of a utility loss of 0.0061 per unit of BMI above 25kg/m2 was applied.

Results for exenatide among patients of average age 59, 10 years duration of diabetes and a baseline of 8.2% HbA1c, 137mmHg systolic blood pressure, a BMI of 32, HDL of 47mg/dL, LDL of 106mg/dL and triglycerides of 199mg/dL over a 35 years time horizon were a discounted life expectancy of 10.66 years and a quality adjusted life expectancy of 7.39, coupled with a lifetime cost of £29,401. The parallel figures for glargine were 10.61 years, 6.95 QALYs and £19,489, yielding a net impact from exenatide of 0.06 life years, 0.44 QALYs and an average cost increase of £9,912 to yield a cost effectiveness estimate of £22,420 per QALY.

Results were sensitive to the assumed utility gain from weight loss: the adoption of CODE-2 time trade-off utilities[246] for the weight gain worsened the cost effectiveness of exenatide to £39,763 per QALY. It was also reported in the text that results were sensitive to the utility assumed for nausea. While the impact of nausea upon cost effectiveness was not separately quantified, it seems likely that the effect of this was encompassed within the £39,763 per QALY figure.

Note that while the Minshall and colleagues[250] study applied long term trends to the progression of HbA1c after a period of initial treatment success, it appears that there was no explicit allowance for progression to insulin therapy within the modelling. Fewer details were provided within the Shaya and colleagues[249] study, but it appears likely that it made similar assumptions.

Watkins and colleagues[253] used the CORE model to compare the anticipated costs and outcomes among the standard UKPDS population and a modified obese population these being identical in terms of most characteristics and an HbA1c of 8.5% at baseline, differing only in weight and the consequences of this for the various risk factors as outlined in Table 31.

Table 31: Obese group compared to UKPDS

	BMI	SBP	Cholesterol	HDL	LDL	Triglycerides
UKPDS population	27.5	135	207	41	134	207
Obese population	35.0	145	217	41	144	230

Both patient groups were assumed to be treated with exenatide. For the UKPDS population this intensification of treatment was assumed to have the CORE default value impacts upon risk factors with there being no change in weight, a rise of 1.3mm in systolic blood pressure, a rise of 1.6mg in LDL levels and a rise of 39mg in triglycerides. When treated with exenatide the obese population was assumed to experience a weight loss of 8.5% or 3 BMI points, a 10mm fall in systolic blood pressure, a 20mg fall in LDL and a 59mg fall in triglycerides. Immediately apparent from this is that it appears to have been assumed that the obese population would have a lower systolic blood pressure, lower levels of LDL and lower levels of triglycerides than the UKPDS population. This raises questions as to the reliability of the modelling, or at a minimum the reporting of the conduct of it within the paper. Unfortunately the paper was also not explicit as to whether any reduction in HbA1c was anticipated for exenatide, though in the introductory sections the authors noted an average reduction of 0.5% to 0.9%.

Treatment with exenatide was compared with the treatments of once daily glargine, pioglitazone, glyburide and no additional treatment. The impact of these treatments was a reduction in baseline HbA1c of 2.0%, 0.6%, 0.9% and 0% respectively, which appears to be likely to have been coupled with the standard CORE reductions in other variables as reported for exenatide use among the UKPDS population. Treatments were assumed to continue for the time horizon of the model.

Among obese patients, exenatide was anticipated to result in cost savings from reduced cardiovascular disease of around US$3,000. Exenatide resulted in higher costs of renal disease by around US$1,000 as compared to glyburide and glargine, but savings of US$2,600 and US$3,800 as compared to pioglitazone and no additional treatment respectively. A similar cost pattern was observed for neurological and ophthalmic costs with exenatide being of around US$1,700 higher cost as compared to glyburide and glargine but around US$1,000 lower cost as compared to pioglitazone and placebo. Cost effectiveness estimates of US$32,000, US$13,000 and US$16,000 per QALY were reported for exenatide against glyburide, glargine and placebo respectively, while pioglitazone was dominated,

though it is not clear whether these estimates were for obese patients or for the patient group as a whole.

As is apparent from the summary above, interpreting the results of Watkins and colleagues[253] is problematic, and it is unclear quite what the cost effectiveness estimates relate to and their reliability is also questionable. It also does not appear that any subsequent intensification of therapy has been considered in patients as time progresses.

The Scottish Medicines Consortium (SMC) issued guidance on exenatide in June 2007, recommending it for restricted use in combination with metformin and/or sulphonylureas. The SMC appraisal was based on an industry submission which used only one trial, that of exenatide versus biphasic insulin.[254] The SMC commented that the comparator of biphasic insulin aspart was more expensive than cheaper forms of insulin, but concluded that additional sensitivity analysis suggested that the ICER against biphasic human insulin would probably be cost-effective.

7.3 DPP-4 inhibitors

7.3.1 Cost effectiveness studies

Schwarz and colleagues[255] explored the cost effectiveness of adding 2nd line sitagliptin to 1st line metformin for patients uncontrolled on a regime of metformin in terms of their HbA1c rising above 6.5%. This was compared on a pairwise basis with two main comparators: (1) adding 2nd line rosiglitazone to 1st line metformin; and (2) adding 2nd line sulfonylurea to 1st line metformin. Those failing on these treatments would progress to metformin plus 3rd line basal insulin, with possible further progression to 4th line multi-dose insulin. For the comparison with adding 2nd line sulfonylurea to 1st line metformin, an additional scenario was modelled with those failing on sitagliptin or sulfonylurea progressing to a 3rd line combination of rosiglitazone and metformin prior to possible progression to insulin therapy as 4th line. For these later therapies, it appears that the same switching threshold in terms of HbA1c was used, though the value for this was varied in sensitivity analyses.

Modelling was undertaken for six European countries, Austria, Finland, Portugal, Scotland, Spain and Sweden, and used the Januvia Diabetes Economic (JADE) model. While the JADE model relied extensively upon the UKPDS Outcomes Model risk equations, it will not necessarily have resulted in the same anticipated patient outcomes as had the UKPDS Outcomes Model been used. The costs of medicines, side effects, direct costs of diabetes related complications and discount rates for both costs and health related quality of life impacts were based upon country specific data, rather than being drawn from the UKPDS Outcomes Model.

The average treatment effects upon HbA1c when added to metformin were differentiated by baseline HbA1c and by comparator treatment as shown in Table 32:

Table 32: Effects on HbA1c according to baseline level

	rosiglitazone comparison		sulfonylurea comparison	
Baseline HbA1c	**sitagliptin**	**rosiglitazone**	**sitagliptin**	**sulfonylurea**
<7%	-0.46%	-0.10%	-0.47%	-0.44%
7-8%	-0.63%	-0.77%	-0.74%	-0.90%
8-9%	-1.04%	-0.86%	-1.35%	-1.41%
>9%	-1.64%	-1.98%	-1.89%	-2.07%

For the comparison with rosiglitazone it was anticipated that sitagliptin would provide an incremental discounted QALY gain of between 0.016 and 0.063, with the cost impact being between a cost saving of €687 to a net cost of €208. For the UK modelling based upon

Scottish data, the patient gain was anticipated to be 0.016 and the incremental cost £25.08 to yield an estimated cost effectiveness of £1567 per QALY.

For the comparison with sulfonylurea in which failures progressed to insulin, it was anticipated that sitagliptin would provide an incremental discounted QALY gain of between 0.037 and 0.095, with the cost impact being a net cost of between €331 and €1097. For the UK modelling, the patient gain was anticipated to be 0.095 and the incremental cost £764 to yield an estimated cost effectiveness of £8,045 per QALY.

For the comparison with sulfonylurea in which failures progressed to rosiglitazone plus metformin prior to insulin it was anticipated that sitagliptin would provide an incremental discounted QALY gain of between 0.045 and 0.103, with the cost impact being a net cost of between €339 and €1130. For the UK modelling, the patient gain was anticipated to be 0.103 and the incremental cost £772 to yield an estimated cost effectiveness of £7,502 per QALY.

The average cost effectiveness of across the modelling was estimated to be €4766 per QALY. Results relative to rosiglitazone were sensitive to the assumed effects of rosiglitazone on cholesterol, systolic blood pressure and the risk of heart failure. Removing the effect upon cholesterol and systolic blood pressure, and halving the increase risk of heart failure saw the cost effectiveness estimate rise to €5012 per QALY, €fall to 2630 per QALY and rise to €6677 per QALY respectively. Varying the utility decrements associated with the long terms complications of diabetes had relatively little impact upon results, a 20% change changing the cost effectiveness estimate by less that €100 per QALY. Varying the costs of these complications had a somewhat larger impact, a 20% change changing the cost effectiveness estimate by less around €700 per QALY. However, for all the sensitivity analyses performed the cost effectiveness estimate remained below €8000 per QALY. Reducing the effectiveness of sitagliptin by 10% had the largest impact, increasing the cost effectiveness estimate to €7548 per QALY.

While the analysis of Schwarz and colleagues[255] did explicitly model the progression to insulin, a limitation of the study may be in considering sitagliptin as a 2nd line treatment rather than as a 3rd line addition to metformin and sulfonylurea prior to patients progressing to 4th insulin therapy as compared to patients progressing directly to insulin therapy as a 3rd line treatment.

Three other papers modelling the cost effectiveness of DPP-4 inhibitors were available only as abstracts: first authors Minshall,[256] Celaya[257] and Fon.[258] Minshall and colleagues considered the cost effectiveness of sitagliptin relative to pioglitazone, while both Celaya and colleagues and Fon and colleagues considered the relative cost effectiveness of sitagliptin, vildagliptin, rosiglitazone and pioglitazone. Minshall adopted a US perspective, while both Fon and Celaya adopted a Mexican healthcare perspective, with it seeming likely that treatments under consideration were 2nd line treatments being added to 1st line metformin for patients failing on metformin alone.

Minshall and colleagues[256] estimated the effectiveness of sitagliptin from a separate study of the effectiveness of pioglitazone, though noted that the baseline HbA1c values were similar between the two studies at 8.04% for sitagliptin and 7.60% for pioglitazone. Daily drug acquisition costs were also similar at US$4.86 and US$4.91 respectively. Given this, pioglitazone was associated with an incremental cost over 35 years of US$359, but also an incremental 0.075 QALYs to yield a cost effectiveness estimate of US$4804 per QALY.

The Fon and Celaya studies[257,258] both relied upon a meta analysis for their estimates of the effectiveness of sitagliptin, vildagliptin, rosiglitazone and pioglitazone. It appears likely that the Celaya paper was a development of the Fon paper, given their similarities and that both lead authors are named authors of the other paper. While it is not explicit within the abstracts, it appears likely that the same meta analysis was used by both, Celaya and colleagues noting that it standardised the baseline HbA1c at 9% across treatments. Both studies adopted a one year perspective, estimating the direct treatment costs, outpatient

visits, inpatient admissions, emergency room admissions and the like to estimate the incremental cost effectiveness and incremental net benefits. Few details were provided within the abstracts, to the extent that the outcome measures were not clear, though it may have been as simple as per unit of HbA1c reduction. Vildagliptin was estimated to have the lowest overall annual treatment cost, US$1,434 within the Fon paper as compared to US$9,176 within the Celaya paper. Vildagliptin was also estimated to have the lowest cost per successful unit US$1,304 in the Fon paper compared to US$8,342 within the Celaya one, these figures both implying an additional 1.10 units of outcome arising from vildagliptin use. The authors concluded that vildagliptin dominated the other treatments. The reasons for the differences in cost estimates between Fon and Celaya were not clear.

The Scottish Medicines Consortium issued guidance on vildagliptin in March 2008[259] and on sitagliptin in September 2008.[260]

The guidance on vildagliptin was based on the Novartis submission, which provided a cost-minimisation analysis comparing vildagliptin with the glitazones. The assumption was that they were equally clinically effective. Costs were over a one-year period. The comparison used the maximum daily dose of rosiglitazone which is not used in the majority of patients in Scotland. However the SMC guidance concluded that using a lower dose would not change the conclusions. The SMC noted that there were limited data, at that time, on some of the assumptions. However vildagliptin was accepted for restricted use. The guidance does not specify any costs per QALY.

The guidance on sitagliptin was based on the Merck Sharp and Dohme submission, which provided two cost-utility analyses, both with a glitazone as the comparator. One was sitagliptin added to metformin and a sulphonylurea, versus a glitazone added to metformin and sulphonylurea. The other assumed that metformin was not tolerated, and compared sulphonylurea plus sitagliptin with sulphonylurea plus a glitazone. The UKPDS model was used. The SMC guidance notes that the main drivers were the congestive heart failure associated with the glitazones, and the cardiovascular risk associated with weight gain – also a feature of the glitazones. The modelling produced very low ICERs at £5,007 and £1,902. The SMC identified some limitations and problems with the modelling, but accepted that the economics case had been demonstrated. The SMC guidances are quite short, and little detail is given.

Economic literature review: Glargine and Detemir

The previous technical assessment report investigating the cost effectiveness of the long acting insulin analogues, TA53, undertook a systematic review of the literature to January 2002 and concluded that “There are no published studies investigating the cost-effectiveness of insulin glargine, or indeed any other insulin analogue. In addition, there are no published studies investigating the cost effectiveness of NPH insulin, the most likely comparator for insulin glargine.”[12]

What follows reviews the cost effectiveness studies of glargine, detemir and NPH among patients with type 2 diabetes arising subsequent to this, though a number of these were only available in abstract or summaries of International Society For Pharmacoeconomics and Outcomes Research (ISPOR) poster presentations. It will become obvious that most of these studies have been funded by the manufacturers, often with co-authors from the companies, and a consistent finding is that the studies funded by manufacturers find their own products cost-effective. The modelling is often well done and thorough, but will not be convincing if based on assumptions which seem unduly favourable to the product under review.

Full papers

Cost effectiveness

The report from the Canadian Agency for Drugs and Technologies in Health (CADTH) by Tran and colleagues includes a cost-effectiveness analysis. However it included no cost-effectiveness studies for type 2 diabetes.[142]

Brandle and colleagues[261] estimated the cost effectiveness of glargine compared with NPH among patients failing on oral anti-diabetics over a ten year time horizon from the perspective of the Swiss healthcare system. Patient characteristics were an average age of 66 years, 9 year duration of diabetes, a BMI of 29.4kg/m2 and an SBP of 155mm. Modelling was implemented through the Diabetes Mellitus Model, the main inputs being two possible effects upon HbA1c for glargine of -0.96%, which was labelled as pessimistic, and -1.24% which was labelled as optimistic, as compared with an assumed effect for NPH of -0.84%. These values were drawn from a single study within the literature. This was that by Fritsche and colleagues[162], details of which are in the clinical effectiveness section of this review. As shown in Figure 2, it reported one of the bigger differences in HbA1c. As a consequence, glargine was seen as having a superior effect on HbA1c of between 0.12% and 0.40%. These relative benefits appear to have been assumed to persist indefinitely, as a common annual increase of 0.1% was applied after the first two years to both glargine and NPH. The HbA1c effects were applied to three patient groups with differing baseline HbA1c levels: 10%, 9% and 8%. Effects upon severe hypoglycaemic events and weight were not modelled.

Within the pessimistic scenario, glargine was seen as costing CHF1,532, CHF1,685 and CHF1,887 more per patient with net patient benefits of 0.038, 0.037 and 0.038 QALYs respectively, resulting in cost effectiveness estimates of CHF49,441, CHF45,701 and CHF49,468 per QALY. Within the optimistic scenario, glargine was seen as saving CHF95, costing CHF350 and costing CHF734 more per patient with net patient benefits of 0.123, 0.123 and 0.128 QALYs respectively, resulting in cost effectiveness estimates of dominance, CHF2,853 and CHF5,711 per QALY.

While these appear relatively favourable cost effectiveness estimates for glargine, the relevance of the study is undermined through the reliance upon a single study for the estimate of glargine having a 0.12% to 0.40% superior HbA1c impact as compared to NPH, and the assumption that this absolute benefit will be maintained through time through the application of a common 0.1% annual increase.

This analysis by Brandle and colleagues was funded by sanofi-aventis, the manufacturer of glargine, and one of the authors was from that company.

A similar study by Maxion-Bergemann and colleagues[262] from the German branch of Aventis Pharma and the consultancy firm, Analytica International, funded by Aventis, also used the Diabetes Mellitus Model, also with similarly favourable assumptions, and also concluded that glargine would give better glycaemic control, and hence reductions in complications, mortality and costs. However they did test the effect of three different levels of improved glycaemia control with differences between NPH and glargine of 0.13%, 0.44% and 0.85% (NB our meta-analysis showed no difference). It is a careful and thorough analysis but all underpinned by what we think are unduly favourable assumptions about HbA1c differences.

Grima and colleagues[263], from Sanofi-aventis and an economics consultancy, funded by the manufacturer, developed their own markov model from data within the literature, mainly the UKPDS papers and the DCCT trial, to assess the cost effectiveness of glargine relative to NPH for both patients with type 1 diabetes and patients with type 2 diabetes. While the paper noted that meta-analysis suggested similar effects from both glargine and NPH upon HbA1c, it was assumed (based on analysis by Yki-Jarvinen and colleagues 2003[264]) that the lower rate of hypoglycaemia with glargine as compared to NPH could be translated into an additional effect upon HbA1c of -0.87% for glargine over and above that observed for NPH. This relative effect was assumed to persist over a patient's lifetime, with a common annual drift on HbA1c of 0.135% being applied to both arms. Patients with type 2 diabetes of average age 53 years were simulated across cohorts of differing baseline HbA1c: 7%, 8%, 9% and 10%+.

The average net cost of glargine as compared with NPH among patients with type 2 diabetes was estimated as Can$1,992. This varied considerably across the cohorts simulated: an additional cost of Can$3,310, Can$2,160 and Can$896 for those of 7%, 8% and 9% at baseline. Within the cohort of more than 10% HbA1c at baseline glargine was found to be cost saving at –Can$320. In terms of patient impact, the net benefit from glargine was estimated to be 0.22, 0.23, 0.24 and 0.25 QALYs as for the four cohorts of HbA1c 7%, 8%, 9% and 10%+ respectively.

Overall, glargine was estimated as conferring an additional 0.25 years survival and a gain of 0.23 QALYs, resulting in acost effectiveness estimate of Can$8,618 per QALY relative to NPH. While the study is interesting in terms of the de novo model structure, the applicability of the conjectured 0.87% relative absolute benefit on HbA1c from glargine over NPH may be questionable. The assumption that this absolute benefit persists over the patient lifetime is also questionable.

McEwan and colleagues in two abstracts and a full paper (funded by Sanofi –aventis and with an author from the company) evaluated the use of glargine from an NHS perspective. The first abstract by McEwan and colleagues[265] assumed that the main impact was on rates of severe, symptomatic and nocturnal hypoglycaemic events, with there being no difference in HbA1c between glargine and NPH. Currie was listed as an author, and it seems likely that the quality of life impacts of hypoglycaemic events were as previously estimated within the paper listing him as first author, and as reviewed within the cost effectiveness modelling chapter below.[266] Given these impacts, the authors estimated cost effectiveness for glargine of £15,197 per QALY.

In the second abstract, of an ISPOR presentation by McEwen and colleagues[267], glargine was anticipated to lead to a 0.21% superior HbA1c as compared to NPH, and also to confer benefits in terms of reduced hypoglycaemia events. Overall, the cost effectiveness of glargine was estimated to be £5,806 per QALY for insulin naïve patients, and £3,415 per QALY for non insulin naïve patients. Excluding the effects upon hypoglycaemic events raised these to £18,179 per QALY and £7,973 per QALY respectively.

In the full paper by McEwan and colleagues[268]), it is noted that the key assumption on HbA1c comes from the same meta-analysis by Yki-Jarvinen and colleagues[264] used in the Grima analysis[263], which probably over-estimates the difference. However McEwan and colleagues also carried out their analysis assuming no difference in HbA1c, but only in the frequency of hypoglycaemia. But the assumptions there were derived partly from a recent meta-analysis carried out for the manufacturer, and not in the public domain. This gave a relative reduction in hypoglycaemia of 40%. But the background rates of hypoglycaemia appear to come partly from studies in type 1, such as the DCCT, which may not be relevant to patients in the situation of just starting insulin.

So again, the underlying assumptions may favour glargine.

Only one full paper evaluating the cost effectiveness of detemir among those with type 2 diabetes was identified: Valentine and colleagues[269], from the IMS consultancy, and Novo Nordisk, the manufacturers of detemir. Modelling was over a 35 year time horizon for an average age at baseline of 62 years, duration of diabetes of 7 years and BMI of 30kg/m2. It appears to have used the CORE diabetes model. The costing perspective was that of the US healthcare system. Clinical effectiveness estimates were drawn from the German part of the PREDICTIVE study, an observational study of 2,000 patients who were uncontrolled on either oral hypoglycaemic agents, NPH plus oral hypoglycaemic agents, or glargine plus oral hypoglycaemic agents, and who were switched to detemir.[270] This anticipated beneficial effects from switching to detemir upon both HbA1c and BMI, and typically also upon hypoglycaemic events, as shown in Table 33:

Table 33: Benefits of detemir as reported by PREDICTIVE

Switching to detemir from	OHA	NPH	Glargine
HbA1c	-1.29%	-0.60%	-0.59%
BMI	-0.138	-0.382	-0.520
Hypoglycaemic events p.a.	+1.17	-6.76	-7.28

Given those assumptions, modelling anticipated that switching to detemir would yield an additional 0.71, 0.35 and 0.34 undiscounted life years as compared to remaining on OHA, NPH and glargine respectively. The impact on discounted QALYs was 0.31, 0.45 and 0.46 which when coupled with net costs of US$2,290, US$2,824 and US$1,834 resulted in cost effectiveness estimates of US$7,412 per QALY, US$6,269 per QALY and US$3,951 per QALY compared to OHA, NPH and glargine respectively.

However some of the improvements could be due a “trial effect” even though the study was not a trial. Patients who were not well-controlled on glargine might have improved their control given more attention, even if left on glargine. The clinical effectiveness estimates for the effect of detemir on HbA1c being superior to those of both NPH and glargine are very favourable to detemir, making the cost-effectiveness results questionable.

Comparative costs.

Two studies compared the costs of care with detemir and glargine. Poole and colleagues,[271] in a study funded by Sanofi-Aventis, and published in a journal supplement sponsored by sanofi-aventis, concluded that;

“Diabetes management with glargine results in markedly reduced costs of diabetes-related treatment compared with detemir in people with type 1 or type 2 diabetes.”

Valentine and colleagues,[272] in a study sponsored by Novo Nordisk, concluded that;

“In comparison with glargine, detemir …reduced direct medical costs and decreased indirect costs…”

Premixed regimens.

While not the focus of the review, two full papers were identified comparing the cost effectiveness of once daily glargine with twice daily premixed insulin [70/30]: Ray and colleagues[273] and Goodall and colleagues.[274]

Ray and colleagues[273] assessed the cost effectiveness of once daily glargine with twice daily premixed insulin among those failing on oral antidiabetic drugs from the perspective of the US healthcare system, using the CORE diabetes model. Baseline patient characteristics were an average age of 52 years, 9 years duration of diabetes, BMI of 31kg/m2 and a baseline HbA1c of 9.77%. Clinical effectiveness estimates were drawn from the INITIATE trial: a 28 week randomised open label US study. The mean reduction in HbA1c within this was statistically significantly greater for premixed insulin than for glargine, the average changes being -2.79% and -2.36% respectively, though premixed insulin was associated with a slightly greater increase in BMI: 1.88kg/m2 as against 1.22kg/m2 for glargine. Premixed insulin was associated with a greater insulin dose increase by end of study to 0.82IU/kg as compared with 0.55IU/kg for glargine.

Results of the modelling were that premixed insulin conferred an additional 0.19 discounted years life expectancy, and by coincidence an identical additional 0.19 discounted QALYs. Total lifetime costs were around 9% higher with premixed insulin at a net cost of $8,824, resulting in a cost effectiveness estimate for premixed insulin of US$46,533 per QALY relative to glargine.

Goodall and colleagues[274] assessed the cost effectiveness of once daily glargine with twice daily premixed insulin among those failing on oral antidiabetic drugs within the Swedish setting, also using the CORE diabetes model. Baseline patient characteristics and clinical effectiveness estimates were drawn from the INITIATE trial and were the same as reported for Ray and colleagues above.

Results of the modelling were that premixed insulin conferred an additional 0.21 discounted years life expectancy, and an additional 0.21 discounted QALYs. The source of the slightly larger net patient benefits as compared with the estimates of Ray and colleagues reported above is not clear, given apparently identical patient characteristics, clinical effectiveness estimates and discount rates. Total lifetime costs were also around 2.5% less with premixed insulin, a saving of SEK10,367, resulting in the authors concluding that premixed insulin dominated glargine.

The modelling of Ray and colleagues and Goodall and colleagues was much the same, but with net costs differing due to a difference balance between the direct treatment costs and the costs of the downstream complications of diabetes. The extent to which they may overstate the relative cost effectiveness of premixed insulin may be influenced by patients on once daily glargine presumably at some point progressing to mealtime insulin, which will not have been captured within the clinical trial.

Cost

While not the focus of this review, two full papers were identified comparing the costs of once daily glargine with twice daily premixed insulin.

Lechleitner and colleagues[275] conducted a prospective observational study among 678 Austrian patients with type 2 diabetes being switched from oral therapy to either once daily glargine with continued oral anti-diabetics or typically twice daily conventional insulin therapy with premixed insulin, though 5% required only once daily injections and 20% required more than twice daily injections. The effectiveness on control of HbA1c was the same for both groups, and as a consequence the study undertook a cost analysis.

Within the glargine group 93% of patients continued their oral therapy regimen, mainly of metformin (43%) and sulfonylurea (43%), while within the conventional insulin therapy group only 46% continued with their oral regime. Probably as a result of this, the median daily dose of insulin was considerably lower in the glargine group at only 16IU as compared with 40IU for the conventional insulin therapy group, thereby introducing a bias. A fairer comparison of the insulins would have kept the oral agents the same, but the triallists were presumably more interested in the total regime. Not surprisingly, the median monthly use of blood monitoring strips was lower in the glargine group at 60 as compared with 80 for the conventional insulin therapy group. In the light of this, the higher cost of glargine was largely offset by lower insulin test strip usage, leading to similar average costs per day: €1.90 for glargine as compared with €1.99 for the conventional insulin therapy group. HbA1c results were 7.8% in both groups.

Janka and Hogy[276] undertook a similar study to Lechleitner above, estimating the cost differences between once daily glargine plus oral agents, against twice daily premixed insulin. Glargine was estimated to have half the annual needle costs, testing strip costs and lancet costs at only €375 as compared with €750 for premixed insulin. This helped offset the additional cost of metformin and glimepride of €346 within the glargine arm. Insulin usage was considerably lower within the glargine arm, being less than half that of the premixed insulin arm, resulting in an insulin cost including pens of around €510 for glargine as compared to €735 for premixed insulin. This resulted in an average annual cost of €1259 for once daily glargine as compared with €1,495 for twice daily premixed insulin. The study was sponsored by, and the author for correspondence was from, sanofi-aventis.

Meeting abstracts.

Thompson and colleagues[277] in an ISPOR poster (co-authors from sanofi-aventis) present the results of cost effectiveness modelling of glargine as compared to NPH. This appears to be a precursor to the full Grima and colleagues[263] paper reported above as the author list is the same, with the same 0.25 QALY gain being estimated from the use of glargine. The estimated cost effectiveness differed slightly at Can$9,804 for reasons that are not clear.

Smith and colleagues[278], in an ISPOR poster presentation from CORE and Novo Nordisk authors, estimated the cost effectiveness of detemir compared to NPH basal-bolus among UK patients with type 2 diabetes from the perspective of the NHS. Clinical effectiveness estimates were not explicitly stated, but it appears to have been assumed that the only significant difference would be in weight with detemir leading to a 0.4kg gain as compared to 1.3kg for NPH. It was noted that detemir has been demonstrated to be non-inferior in terms of both HbA1c and hypoglycaemic events. The modelling predicted a survival gain of 0.13 years from detemir and a gain of 0.08 QALYs, for an additional cost of £1,534: yielding a cost effectiveness estimate of £19,218 per QALY for detemir relative to NPH.

Valentine and colleagues, in an ISPOR presentation[279] (CORE and Novo Nordisk) appear to have undertaken a similar cost effectiveness analysis for detemir as that reported above for their full 2007 paper[280], but only for the subset of those transferring from NPH to detemir. An additional 0.30 QALYs was anticipated from the transfer to detemir, though in this analysis it was also anticipated to be cost saving by US$2,416 due mainly to reduced severe hypoglycaemic events, coupled with lower rates of retinopathy and cardiovascular complications. An additional 2006 ISPOR poster presentation by the same authors[281] concluded that over a 5 year time horizon detemir would result in an additional 0.17 QALYs as compared with NPH, with a cost effectiveness of US$25,368 per QALY.

A third ISPOR poster presentation by Valentine and colleagues[269] (Novo Nordisk and the consultancy, IMS, which took over CORE), 2007, considered the cost effectiveness of patients transferring from glargine to detemir. Clinical effectiveness estimates were as for their full 2007 paper but costs were from the German perspective. Cost savings of €1,032 were anticipated from the conversion to detemir among those failing on glargine, alongside a gain of 0.29 QALYs. The reason for the lower QALY gain compared with their full 2007 paper is not apparent.

In a like manner to the poster presentations of Valentine and colleagues summarised above, Palmer and colleagues[282] (CORE and Novo Nordisk) 2006 in an ISPOR poster presentation appear to have undertaken a similar cost effectiveness analysis for detemir as that within the Valentine and colleagues full 2007 paper, but for the subset of those transferring from orals to detemir. Transferring to detemir was estimated to result in an additional 0.17 QALYs at minimal total cost to yield a cost effectiveness estimate of US$657 per QALY. Within this, transfer to an insulin other than detemir for those failing on orals does not appear to have been considered, which is a major weakness.

Palmer and colleagues[283] (sponsorship not given, but several authors also authors of the Ray and colleagues paper, from Novo Nordisk and CORE) estimated the cost effectiveness of premixed insulin compared to glargine from the US Medicare perspective using clinical effectiveness estimates from the INNOVATE trial. As such it mirrors the results of the full paper of Ray and colleagues reported above273, though estimates a slightly lower gain of 0.15 QALYs but also a slightly lower incremental cost effectiveness ratio of £39,000 per QALY for premixed insulin as compared to glargine.

8 Chapter 8: Cost effectiveness modelling of the new drugs

8.1 The UKPDS Outcomes model

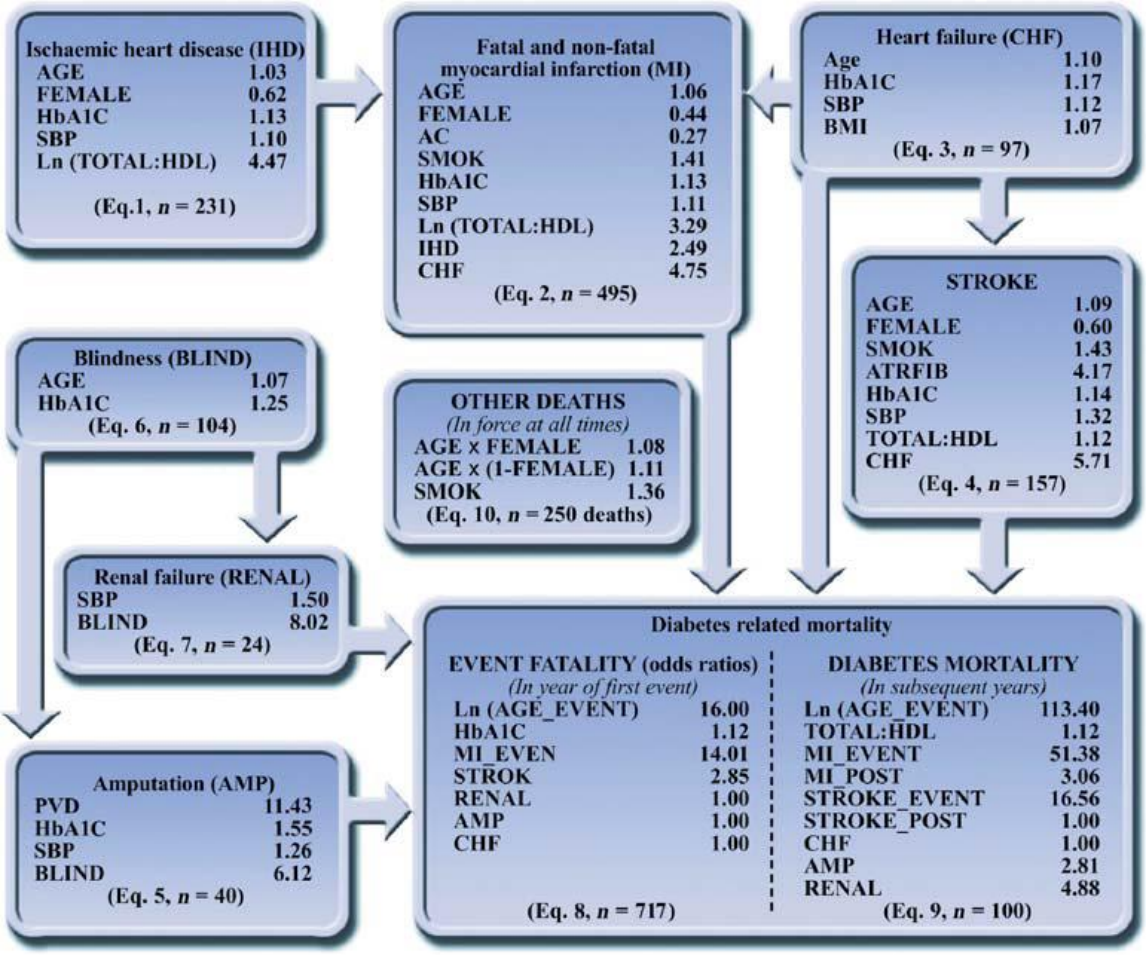
As summarised by Clarke and colleagues,[284] the UKPDS Outcomes model is a lifetime model that aims to estimate the first occurrence of a number of diabetes complications: MI which may or may not be fatal, ischaemic heart disease, stroke, congestive heart failure, amputation, renal failure and blindness in one eye. The likelihoods of complications were estimated from the data of the 3,642 patients with type 2 diabetes who took part in the UKPDS. The utilities and costs associated with complications and with routine ongoing care are included within the model, having also been estimated from the UKPDS population. These are discounted at rates specified by the user.

The likelihoods of complications occurring are functions of patient characteristics, some of which are time varying and projected by the model, and past complications history. The main time varying factors are HbA1c, systolic blood pressure and the ratio of total cholesterol to HDL cholesterol, their evolution being estimated using panel data and random effects modelling. Past complications cascade through the model, in that:

- IHD increases the risk of MI
- CHF increase the risk of MI, stroke and death
- Blindness increases the risk of renal failure and amputation
- MI, stroke, renal failure and amputation all increase the risk of death

As per Figure 15 below:

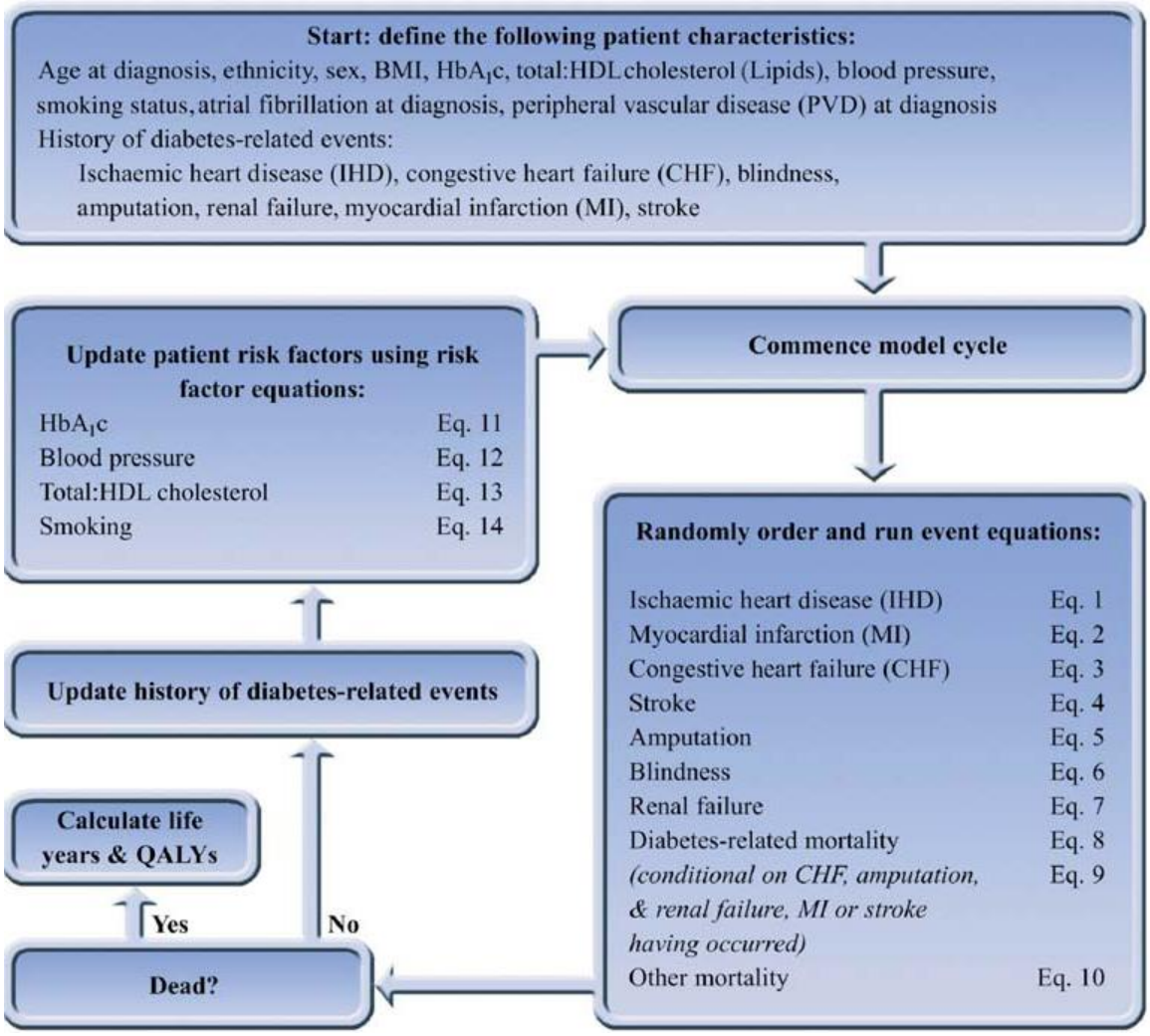
Figure 15: The UKPDS model algorithm (taken from Clarke and colleagues, 2004)



For example, a one point increase in a patient's BMI increases the annual risk of heart failure (CHF) by a factor of 1.07, while a 1% point increase in a patient's HbA1c increases the annual risk of CHF by 1.17. As can be seen from the above, a patient's BMI has limited direct impact, affecting only the likelihood of CHF as already outlined. However, this is because most of the effect of BMI is mediated through changes in systolic blood pressure and the total cholesterol to HDL cholesterol ratio. But should CHF occur the effects cascade through the model, increasing the risk of MI, stroke and death.

The implementation of the model is also most easily seen through reference from the figure within Clarke and colleagues in Figure 16:

Figure 16: The UKPDS model equations (taken from Clarke and colleagues, 2004)



Limitations to the model, as noted in Clarke and colleagues[284], are that:

- It only estimates the first event (strictly speaking, the first new event, since patients may have had past events)
- Not all complications are modelled; e.g. peripheral neuropathy
- Hypoglycaemic events are not modelled
- Quality of life impacts are derived only from complications

Note that within the model it is possible to specify the evolution of risk factors such as HbA1c through time, and as a consequence the effect of intensification of treatment from oral agents to basal insulin, and from basal insulin to basal/bolus insulin upon these risk factors can be specified even if these intensifications occur some time after baseline.

Other parameters such as weight can be specified for the baseline as patient characteristics. For these parameters an initial treatment effect can be implemented between treatments; e.g. for exenatide versus glargine, by specifying the baseline value for exenatide to be equal to the baseline value plus initial treatment effect for exenatide while for glargine to be equal to the baseline value plus initial treatment effect for glargine. But these parameters cannot be altered at any intensifications of treatment after baseline. This is also common to other models of diabetes, such as the Economic Assessment of Glycemic control and Long-term Effects EAGLE model [285], and the CORE model.[286] This has implications for comparing treatments with different effects on weight.

The UKPDS Outcomes Model [284] is a patient level simulation model which provides the point estimates in terms of average life expectancy, quality adjusted life expectancies, and the costs of complications using a set of central parameter values to predict the likelihood of diabetes-related complications occurring given various patient characteristics. The model also outputs the central estimate of the cumulative mortality through time, this again being based upon the results of modelling using the set of central parameter values. Due to the patient level simulation approach, a number of iterations of the model have to be performed in order to reduce variability within the estimates and achieve convergence for the point estimates; i.e. for each treatment regime simulated for a given patient the model performs a number of iterations to achieve convergence for the point estimates for that one treatment-patient combination.

To illustrate the impact of the number of iterations and their effect upon convergence of model estimates, the impact of increasing the number of iterations upon the standard deviation as a percentage of the average value of the model outputs across 1,000 identical patients can be examined as below. Within this, the patient characteristics for each of 1,000 patients was taken to be as outlined for the male patient with a BMI of 35kg/m2 receiving exenatide followed by glargine upon the intensification to insulin at year 6, as outlined later in this chapter. For current purposes the patient characteristics are secondary to the illustration of the impact of increasing the number of iterations upon the standard deviation of the estimated outputs, as shown in Table 34.

Table 34: Effect of number of iterations on convergence

Model iterations	1,000	10,000	100,000	250,000
s.d.[QALYs]/E[QALYs]	1.27%	0.44%	0.24%	0.18%
s.d.[costs]/E[costs]	6.65%	2.14%	0.67%	0.44%

Given the above and computational availability, 250,000 iterations will be performed in order to approach convergence. However, there remains small variability across estimates as shown above. The size of this variability should be borne in mind when examining the results of the modelling and their practical significance, even given 250,000 iterations having been applied.

The UKPDS Outcomes model incorporates, and allows the user to modify, the following: the immediate costs of routine care excluding the immediate drug therapy costs, the immediate and long-term the costs of complications and the quality of life impact of the complications modelled. It does not provide a ready means of including other costs or effects , but it does output point estimates through time of the cumulative mortality for a given treatment simulation. As outlined below there are a range of other inputs to the modelling that need to be included: the drug therapy costs and the costs of switching to insulin, and the direct quality of life impacts arising from nausea, severe hypoglycaemic events and weight changes. These will be appended to the output of the UKPDS Outcomes Model in a deterministic fashion, annual quantities being conditioned by the proportion of patients remaining alive within the relevant year, prior to being discounted at the 3.5% as recommended by NICE. For ease of reference, these will be described as the “bolt-ons”.

It should be noted that the UKPDS Outcomes Model also has a facility to perform additional runs of the model for a set of up to 999 bootstrapped sets of parameter values. This facility can be used to characterise the 2nd order uncertainty around the outputs of the model. This facility has not been used for the current review for two reasons.

- Firstly, full characterisation of 2nd order uncertainty would also require characterisation of the 2nd order uncertainty around treatment effectiveness parameters, which is not easily implementable alongside the bootstrap function. It might also conflict to a degree with the reliable elimination of 1st order uncertainty.
- Secondly, given the centrality of the point estimates of cumulative mortality and resultant survival function to the estimated effect of the “bolt-ons”, aligning the three aspects of the

modelling: the model point estimates, the bootstraps and the “bolt-ons”, would be complicated. The “bolt-ons” rely upon the estimated survival function, and as a consequence require that the point estimates be used.

8.2 Methods

8.2.1 Patient population modelled

The previous clinical guideline (CG66) drew patient baseline characteristics from expert opinion rather than the UKPDS, as this was felt to be more likely to reflect those moving on to third line therapy.6 These were broadly in line with the inputs to the modelling reported in the economic literature above, and will be adopted for the current modelling. Note that within this, the representative patient is assumed to have progressed from metformin, to combined metformin and sulfonylurea, but now to having poor control as defined by HbA1c rising above 7.5%. Given this worsening of control, there is a choice as to how to intensify therapy with the newer agents such as exenatide, vildagliptin and sitagliptin, older ones such as rosiglitazone and pioglitazone, and the insulins, glargine, NPH and detemir, all being possible options.

Table 35 shows baseline characteristics of patient populations.

Table 35: Baseline characteristics of patient population: male and female

Characteristic	Value	Value
Sex	Male	Female
Age	58 years	58 years
Duration of diabetes	5 years	5 years
HbA1c	7.5%	7.5%
Height	170cm	165cm
Weight	87kg	82kg
BMI	30kg/m2	30kg/m2
SBP	140mmHg	140mmHg
Total cholesterol	4.4mmol/l	4.4mmol/l
HDL Cholesterol	1.0 mmol/l	1.0 mmol/l

Note that male and female patients will be modelled separately. Being typically slightly shorter, for a given BMI the average female patient weight will be slightly less. Since the BMI modelled is the same for both male and female patients, any differences in the output of the UKPDS Outcomes Model are anticipated to be a pure sex effect.

Similarly, since insulin dosage is weight dependent and BMI has some, though limited, impact upon the outcomes of the UKPDS Outcomes Model, the impact of weight upon cost effectiveness will also be explored through applying a BMI of 35kg/m2.

For a given BMI and insulin dose per kg, women will also require a lower overall insulin requirement.

The previous guideline did not outline the background prevalences of complications associated with diabetes. The THIN study[287] outlines rates of complications for those transferring to insulin therapy, using data from a large UK general practice database. Adopting the rates of complications as reported for the HbA1c≥7% would imply prevalences as shown in Table 36

Table 36: Baseline morbidity

Morbidity	Prevalence assumed	Source
Congestive HF	3.7%	UKPDS284 and THIN287
Amputations	0	UKPDS
Neuropathy	6.5%	THIN
Blindness	0	UKPDS
Retinopathy	17.7%	THIN
ESRF	0	UKPDS
Nephropathy	0.7%	THIN
Stroke	4.9%	THIN
MI	8.2%	THIN

However, it should be noted that a proportion of patients within this group would have had somewhat worse HbA1c levels than is being assumed within the baseline UKPDS patient characteristics. There may also have been some correlation among these, with some patients having more than one complication. This is not easily accounted for within the UKPDS Outcome model, and as a consequence the base case will first model using an assumption of no complications at entry. Since we know from the UKPDS that many (about 25%) had complications at entry, this will be followed by with an analysis assuming the above complication rates coupled with a further assumption that patients with one complication did not have another concurrently. This latter analysis may provide an upper estimate since: the rates of complications may be too high for the group modelled; and, the likelihood is that some patients had a range of comorbidities and while these patients would do relatively poorly this would be more than balanced by other patients having no comorbidities and performing rather better.

It is worth noting also that the UKPDS excluded newly diagnosed patients who had had recent MI, or who had angina.

8.2.2 The comparator treatments: direct head to head comparisons

As previously noted, all patients reaching this stage have failed on dual oral therapy, usually with metformin and a sulphonylurea, and so the issue is which drug to add as third line. Given the clinical effectiveness review, the comparisons chosen for modelling are:

1. Exenatide and glargine (as reported above in the summary of Heine and colleagues[53])
2. Sitagliptin and rosiglitazone (as reported above in the summary of Scott and colleagues[120])
3. Vildaglitpin and pioglitazone (as reported above in the summary of Bolli and colleagues[122])
4. Glargine and NPH insulin (as reported within the meta analysis in Chapter 4)
5. Detemir and NPH insulin (as reported within the meta analysis in Chapter 4)

This gives rise to the following clinical effectiveness estimates for the modelling for the base case male patient with a BMI of 30kg/m2 of: (see Table 37)

Table 37: Inputs to model

	Comparison 1		Comparison 2		Comparison 3	
	exenatide	**glargine**	**sitagliptin**	**rosiglitazone**	**vildagliptin**	**pioglitazone**
HbA1c (%)	-1.11%	-1.11%	-0.79%	-0.76%	-0.88%	-0.98%
Weight (kg)	-2.3	+1.8	-0.4	+1.5	+0.3	+1.9
Nausea	57%	9%	1%	1%	..	..

	Comparison 1		Comparison 2		Comparison 3	
Severe hypos	0.3 p.a.	0.3 p.a.	..	..	0	0
Nocturnal hypos		2.67RR				

	Comparison 4		Comparison 5	
	glargine	**NPH**	**detemir**	**NPH**
HbA1c (%)	Same effect		+0.08%	
Weight (kg)	-0.28		-1.20	
Nausea	..	..	..	..
Severe hypos	0.82RR		0.76RR	
Nocturnal hypos	0.56RR		0.61RR	

Note that within these comparisons many of the differences in point estimates did not reach statistical significance. Also note that the comparison of exenatide and glargine is based upon the results of Heine and colleagues.[53] The results of Barnett and colleagues[50] would imply relatively greater effect from exenatide upon severe hypoglycaemic events but a relatively lesser effect upon patient weight. Given the results of Barnett colleagues, the effect upon BMI will be taken to apply across the other patients simulated.

8.2.3 Insulin Doses

A distinction between the newer drugs such as exenatide and the insulins is that the insulin dose is weight dependent. There is also evidence that the insulin dose increase with patients' BMIs, (as shown in Figure 17) from data from the Aberdeen Diabetic Clinic.(unpublished)

Figure 17: Mean insulin dose per day versus BMI

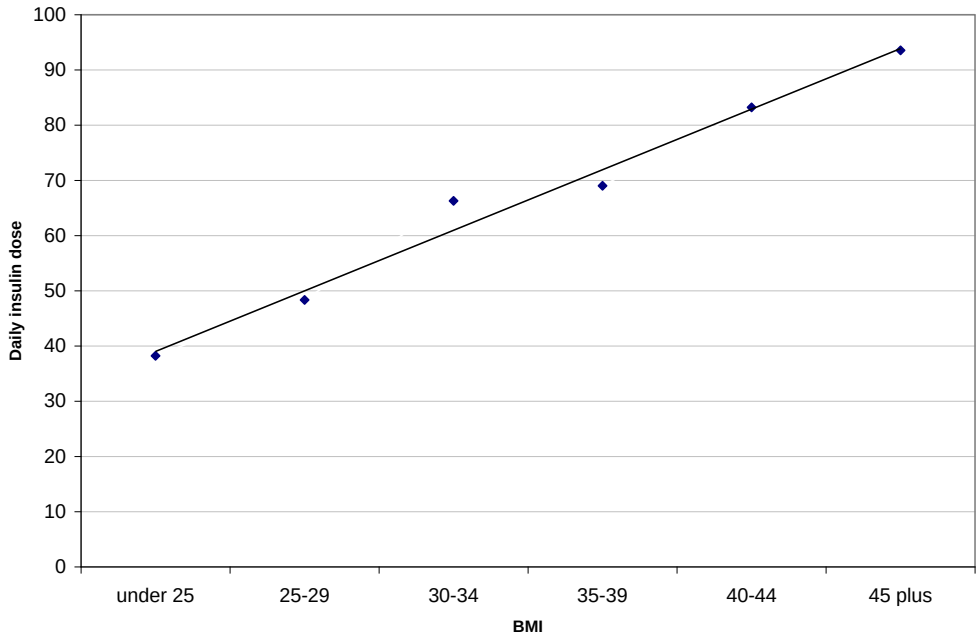


Figure 17suggests an average requirement for the base case of around 0.55 IU/kg/day. Patients with BMIs in the mid 30s would require a higher dose of around 0.65 IU/kg/day

8.2.4 Direct drug costs

The annual direct drug costs and monitoring of the various regimes are valued using BNF 56[288] resulting in costs for a male patient of BMI 30 kg/m2 are shown below in Table 38

Table 38: Direct drug costs

Met+Sulf+Exenatide	
Metformin 2g/day	£ 26.07
Gliclazide 160mg/day	£ 20.56
Exenatide bid	£ 830.25
snap-on needle cost	£ 31.10
Annual total	£ 907.98

Met+Sitagliptin	
Metformin 2g/day	£ 26.07
Sitagliptin 100mg/day	£ 433.57
Annual total	£ 459.64

Met+Vlidagliptin	
Metformin 0g/day	
Vildagliptin 2*50mg/1mg Met	£ 386.41
Annual total	£ 386.41

Met+Sulf+Rosiglitazone	
Metformin 0g/day	£ -
Gliclazide 160mg/day	£ 20.56
Rosiglit. 8mg+Met(2*4mg/1mg)	£ 481.80
Annual total	£ 502.36

Met+Sulf+Pioglitazone	
Metformin 2g/day	£ 26.07
Gliclazide 160mg/day	£ 20.56
Pioglitazone 30mg/day	£ 437.22
Annual total	£ 483.85

Met+Sulf+Glargine	
Metformin 2g/day	£ 26.07
Gliclazide 80mg/day	£ 10.28
Glargine 0.55U/kg/day	£ 452.53
pen	£ 5.15
needles	£ 31.10
Monitoring Strips 1	£ 109.50
Annual total	£ 634.63

Met+Sulf+NPH	
Metformin 2g/day	£ 26.07
Gliclazide 80mg/day	£ 10.28
NPH Average 0.55U/kg/day	£ 284.09
pen	£ 6.89
needles	£ 31.10
Monitoring Strips 1	£ 109.50
Annual total	£ 467.93

The ingredient cost per unit of detemir is the same as for glargine, but there is evidence of there being an estimated 18% higher dosing requirement for detemir in type 2 diabetes as compared to glargine. With a slightly higher cost per pen, this yields a cost for detemir of £716.09 as compared with the £634.63 for glargine shown above. Note that while the non-insulin regimens postpone the need for insulin, they do not prevent the need for insulin eventually. For example, the UKPDS model indicates that given the initial HbA1c effect from exenatide, the patient's HbA1c will progressively worsen until after 5 years, the 7.5% threshold will be reached, triggering an intensification of treatment, with a switch to insulin.

For those intensifying to mealtime insulin it will be assumed that the dose of insulin increases by 0.2IU/kg/day with the regimen costs, shown in Table 39, estimated as:

Table 39: Cost of insulin regimens

Met+Glargine+Bolus	
Metformin 2g/day	£ 26.07
Glargine 0.55U/kg/day	£ 452,53
pen	£ 5.15
needles	£ 31.10

Met+NPH+Bolus	
Metformin 2g/day	£ 26.07
NPH 0.55U/kg/day	£ 284.09
pen	£ 5.15
needles	£ 31.10

Short Acting 0.2U/kg/day	£ 121.82	Short Acting 0.2U/kg/day	£ 121.82
pen	£ 6.19	pen	£ 6.19
needles	£ 31.10	needles	£ 31.10
Monitoring strips 1	£ 109.50	Monitoring strips 1	£ 109.50
Annual total	£ 783.47	Annual total	£ 616.76

Again, it will be assumed that detemir requires an additional 18% dose as compared with glargine, leading to a cost of £864.92 as compared to the £783.47 as reported above for glargine.

For a female patient of BMI 30kg/m2, the slightly lower average weight due to slightly lesser average height slightly reduces the average costs of the insulin containing regimes. Similarly, increasing the BMI of male and female patients to 35kg/m2 increases the costs of the insulin containing regimes, due to both the greater weight of the patient and the higher dose require per kilogram (see Table 40).

Table 40: Costs of drug regimens by BMI

	Female BMI 30	Male BMI 35	Female BMI 35
Metformin + sulfonylurea + glargine	£608.41	£806.05	£769.88
Metformin + sulfonylurea + NPH	£451.46	£575.54	£552.83
Metformin + sulfonylurea + detemir	£685.14	£918.36	£875.69
Metformin + glargine + bolus	£750.18	£975.19	£930.79
Metformin + NPH + bolus	£593.24	£744.68	£713.74
Metformin + detemir + bolus	£826.91	£1087.50	£1,036.59

8.2.5 Other costs of treatment

In addition to the above costs, transferring to insulin requires patient education in the use of pens and titration of dosage over time, which involves specialist nursing time with an associated cost. If it is assumed that this requires an additional 15 minutes of nurse time for training in blood glucose monitoring, 30 minutes in the use of pens plus two follow up phone calls this would amount to roughly an additional hour of a senior nurses time: currently costed by the PSSRU at £60 per hour.[289] More conservatively, the 2006-07 reference costs state the average cost per non-consultant led outpatient attendance for diabetic medicine as being £84, which when combined with the additional follow up phone calls would suggest an overall cost of £178. £178 will be used for the base case. Note that this contrast with the fixed doses of exenatide, where the only change is the doubling from half dose to full dose to minimise early side-effects.

The costs of the complications of diabetes as estimated within the UKPDS Outcomes model are intrinsic to the model, having been estimated from UKPDS data (see Table 41). These will be uprated from 2004 prices to 2007 prices using the PSSRU Hospital & Community Health Services Pay and Prices Index, this showing a general inflation of 12% over the period as below.[289]

Table 41: Costs of complications

	At time of event		Annual thereafter
	Fatal	Non-fatal	
IHD		£3,020	£998
MI	£1,530	£5,823	£959
Heart failure	£3,368	£3,368	£1,180
Stroke	£4,492	£3,562	£673
Amputation	£11,596	£11,596	£670

	At time of event		Annual thereafter
	Fatal	Non-fatal	
Blindness		£1,521	£644
Renal failure	£33,600	£33,600	£33,600

Similarly, in the absence of complications the annual costs excluding the costs of therapy will be drawn from the UKPDS Outcomes Model and inflated to £419.

8.2.6 The quality of life impacts of complications within the UKPDS Outcomes Model

For the quality of life impacts of the complications modelled, the UKPDS Outcomes model applies the following decrements to a baseline average quality of life of 0.785 (see Table 42).

Table 42: Utility decrements from complications

	Utility Decrement
IHD	-0.090
MI	-0.055
Heart failure	-0.108
Stroke	-0.164
Amputation	-0.280
Blindness	-0.074
Renal failure	-0.263

8.2.7 The evolution of HbA1c within the modelling

The new drugs such as exenatide and the gliptins may postpone the transfer of patients to insulin. However, the assumption will be one of postponement rather than avoidance. Given this, there will be a sawtooth pattern to the evolution of HbA1c from the new drugs, with their initial reduction in HbA1c being followed by a slow rise as beta cell function declines.

The evolution of HbA1c will be that projected by the UKPDS Outcomes model. But as advised by the GDG, treatment will be intensified when HbA1c rises above 7.5%. If this implies a switch to insulin therapy, a treatment effect as outlined in the summary of model inputs will be assumed depending on the insulin regimen adopted. If treatment intensification is to add mealtime insulin to basal insulin an initial effect of a 0.5% improvement in HbA1c will be assumed. Note that within the implementation of the UKPDS Outcomes model, it will be assumed that patients will rise above the 7.5% intensification threshold. The HbA1c effect of treatment intensification will be assumed to apply for the year subsequent to this, with the evolution of HbA1c being that projected by the UKPDS Outcomes model thereafter. This gives rise to a sawtooth evolution

The evolution of HbA1c under different treatments requires consideration, and for some drugs, long-term data are not available.

The UKPDS showed progression of disease irrespective of which drug was used. That study used two sulphonylureas, metformin and insulin. It has been suggested in the “durability” study29 that progression might be slower on a glitazone than a sulphonylurea, but if true, that would not be relevant here, because the glitazone would be used after the sulphonylurea, and the relevant comparison would be with a gliptin or exenatide.

Despite assertions that exenatide or the gliptins might preserve beta cell function, the evidence from studies in which these drugs have been used and then withdrawn, show no lasting effect. We will therefore assume that there are no differences in progression rates amongst the glitazones, the gliptins, exenatide or the insulins. (Note that the UKPDS did not report on progression according to weight loss – those with dramatic weight loss might have

been expected to show slower, or no, progression. However dramatic weight loss is not common enough to be relevant here.)

However the evolution of HbA1c may be different with insulins. Take for example, the comparison of exenatide and glargine as third line therapy (i.e in addition to metformin and a sulphonylurea).

After exenatide is started, there is a fall in HbA1c of about 1.1%, after which HbA1c slowly rises because of progression of disease, and because the dose is fixed. After about five years, HbA1c reaches 7.5%, triggering intensification with a switch to long-acting insulin, with a drop in HbA1c of about 1%.

If glargine is started rather than exenatide, there is the same 1.1% fall, but with some differences. The dose needs to be titrated, so the fall may occur more slowly. However the dose of glargine can be increased further (unlike fixed dose exenatide). So when HbA1c starts rising, the dose of glargine can be increased further, so that the rise in HbA1c should be slower with glargine than exenatide (though possibly at the cost of further weight gain).

Hence over the first period, the rising curve for HbA1c on exenatide might be expected to stay above that for glargine. The 7.5% threshold for intensification will be reached sooner with exenatide than glargine, and the exenatide group may switch to glargine sooner than the glargine group require to intensify to basal/bolus.

This may not apply if those on exenatide lose a lot of weight and those on glargine gain a lot.

Many of those on glargine, whether as third line, or as fourth line after a period on exenatide, will still progress to requiring intensification, because with disease progression and loss of beta cell capacity, they will be unable to control post-prandial glucose with only a basal insulin (or will do so only at the cost of troublesome hypoglycaemia). When they do progress to a basal/bolus insulin regimen, they will experience another “saw-tooth” drop in HbA1c, after which that will be controlled by titration of the meal-time insulin.

Since both the exenatide and glargine groups are assumed to progress at the same rate, their HbA1c curves will in time come to converge. Any differences in areas under the curves will be temporary. We lack data on the difference – there may be a slightly higher curve with exenatide - and it may not be clinically significant over a life time.

Note that where the figure for HbA1c during any year is only marginally less than 7.5%, but where the UKPDS Outcomes model would project it to increase somewhat above this during the following year, the intensification of therapy will be assumed to occur during this following year. This avoids introducing what seems likely to be spurious gains from one treatment postponing the intensification of therapy by an additional year as compared to another treatment when the modelled evolution of HbA1c is only very marginally different between the two treatments.

The reductions in HbA1c observed in the three trials in Table 11 should not be used to conclude that, for example, vildagliptin was more potent than sitagliptin, or pioglitazone than rosiglitazone, because there were no head to head comparisons, and the baseline HbA1cs in the trials were different. For our base case, we have to assume that in terms of glucose lowering effects, there are no significant differences amongst any of sitagliptin, vildagliptin, pioglitazone or rosiglitazone

8.2.8 The evolution of weight within the modelling

As noted within the section describing the UKPDS outcomes model, the weight of a patient at baseline and as modified by the initial treatment intensification can be specified by the user (with the necessary mechanism of assuming that weight change is immediate), but unlike other input parameters its evolution through time cannot be. As a consequence, though HbA1c can be specified to change as patients intensify treatment and move from, say,

exenatide to glargine, to glargine plus mealtime insulin, the patient weight cannot be specified to change and remains principally determined by the value set at baseline. So while the initial fall in weight on exenatide can be entered explicitly within the UKPDS Outcomes model, the subsequent gain after the switch to insulin cannot be.

This may tend to bias the analysis in favour of those treatments which tend to reduce patient weight from the baseline value. For example, exenatide is anticipated to give a weight loss of 2.3kg. This will affect both the likelihood of developing CHF as estimated through the UKPDS Outcomes Model, and the direct quality of life effect of weight changes. But when the patient intensifies treatment and moves from exenatide to insulin, it is not possible to dial this weight loss effect out of the UKPDS Model. It can only be reversed for the direct quality of life effect of weight change. As a consequence, a sensitivity analysis will explore the effect of equalising patient weights at baseline within the UKPDS Outcomes model and only exploring the effects of weight differentials associated with concurrent treatments through their direct impact upon quality of life as outlined below.

8.2.9 The impact of weight changes and nausea

Applying the estimates of the impact of weight upon quality of life as reported in Baghust and Beale [246] to the results of Heine and colleagues[53] suggest that the weight loss associated with exenatide would result in a direct quality of life increment of 0.005. This compares with a quality of life loss of around 0.004 for the weight gain associated with glargine a net treatment effect of a gain of in quality of life from the use of exenatide over glargine of a little under 0.01 arising from the weight dimension alone. At mean weight loss values, the parameter estimate of Coffey and colleagues[247] would not anticipate any quality of life impact though this is due to the dichotomous nature of the variable, which is of only limited applicability to the scenario described.

Among the 82 week completer cohort as reported in Blonde and colleagues[244] the changes in BMI can be inferred if a common height of 1.68m is assumed across categories. This would imply a quality of life increment of around 0.004, 0.006, 0.009, 0.010 and 0.014 for the baseline categories of BMI<25kg/m2, 25kg/m2<BMI<30kg/m2, 30kg/m2<BMI<35kg/m2, 35kg/m2<BMI<40kg/m2 and BMI>40kg/m2 respectively.

The above does not take into account the effects of nausea as reported within Heine and colleague[53]. At the 26 week point 57% of exenatide patients had experienced nausea as compared with 9% of glargine patients. Given the weight loss of 2.63% on average (ratio of mean weight loss and baseline weight) from exenatide, and quality of life increment estimates as reported within the exenatide SMC submission, this suggests that those on exenatide had a quality of life increment of a little less than 0.020 for the 43% not experiencing nausea , as compared to a quality of life decrement of a little less than 0.028 for the 57% who did have nausea, giving a net effect of an average slight utility decrement among those trialling exenatide of a little less than 0.007. The parallel utility decrements for the 91% of glargine patients not experiencing nausea but seeing an average weight gain of 2.05% would be perhaps around two thirds the -0.044 associated with a 3% weight loss. The remaining 9% experiencing both a 2.05% weight gain and nausea might experience a similar fraction of the -0.073 quality of life decrement estimated for those gaining 3% weight and experiencing nausea, as within the SMC submission. (N.B. we have accepted the frequency of nausea as reported by the study. The 9% may seem high for those on insulin use, but “nausea” is probably used to cover a range of feelings, and the opinion of the GDG indicated that though the precise rate might differ according to definition, the absolute difference between exenatide and insulin appeared correct. Note that this is incident not prevalent nausea, so one episode in the six months is enough for patients to be includd in the 9%).

However, the quality of life increments due to weight change as reported in Lilly’s exenatide SMC submission are considerable higher than those of Baghust and Beale.[246] For instance, given a patient height of 1.68cm and a BMI of 31kg/m2, for patients not experiencing nausea

the Baghust and Beale estimates would imply a quality of life increment of around 0.006 for a 3% weight loss and of around 0.010 for a 5% weight loss, these estimates being roughly symmetric for weight gains. The quality of life increments from weight loss as reported within the exenatide SMC submission are around three to four times those of Bagust and Beale, while for weight gains are around seven to eight time those of Bagust and Beale.

It can also be noted that economic appendix of the NICE guideline on obesity[290] applied the following utility modifiers within the economic modelling, as shown in Table 43.

Table 43: Utilities used in NICE obesity guideline

BMI (kg/m2)	Male	Female
< 21	0.86	0.85
21–25	0.87	0.87
26–30	0.86	0.82
31–39	0.82	0.78

These would suggest that a move from the mid-point of the 26-30kg/m2 to the mid point of 31-39kg/m2, an increase of 7 points on the BMI scale, would be associated with a 0.04 loss, or around -0.0057 per BMI point. This is very similar to the -0.0061 per BMI point as estimated for those with type 2 diabetes by Baghust and Beale.[246]

For the base case it will be assumed that nausea is mainly experienced during the first three months of treatment with exenatide, which from a quality of life decrement of 0.048 implies a QALY loss of 0.012. Given the results of Heine and colleagues[53], it will be further assumed that a net 50% of patients treated with exenatide will experience nausea, implying an average QALY loss of 0.006 from treatment with exenatide.

The direct utility effect of weight changes associated with the different therapies will in the base case be assessed using the parameter estimates of Bagust and Beale.[246] As noted above, the new non-insulin therapies will be assumed to postpone treatment with insulin but not prevent it. In assessing the direct utility effect of weight changes, upon transferring to insulin it will be assumed that any weight loss associated with the non-insulin will be reversed and will also be coupled with the weight gain associated with the transfer to insulin.

Note that to apply these quality of life impacts from weight changes, the treatment sequences modelled and associated weight changes need to be conditioned by the survival curves as modelled by the UKPDS Outcomes model i.e. the quality of life effect of any weight change associated with treatment is applied only to the surviving cohort. From this, it is possible to vary the quality of life increments and decrements arising from weight changes to reflect the treatment sequence; e.g. a patient initially using exenatide would experience the quality of life impact of a 2.3kg fall in weight while on exenatide, but when switching to glargine would experience the quality of life impact of returning to the baseline weight and putting on an additional 1.8kg. (NB These trial-based data may under-estimate differences in routine care and longer follow-up, which may be larger).

Furthermore, within this calculation, in the absence of other information, the switch to mealtime insulin is assumed to cause the same weight gain as with glargine. This latter assumption may cause a slight bias against detemir within the indirect comparison with glargine, given that the weight gain from glargine as drawn from the indirect comparison appears slightly greater, though it seems unlikely to have a significant impact upon the comparisons between non-insulin regimes, being a common factor to all. But in general the possible differences between the permutations of weight gain upon the switch from basal to basal bolus insulin seem likely to be slight.

8.2.10 The impact of severe hypoglycaemia events

The UKPDS outcomes model does not permit the direct evaluation of changes to rates of severe hypoglycaemic event rates. But in the technology appraisal (TA53) of long-acting insulin analogues (at that time only glargine), the NICE Appraisal Committee accepted that both hypoglycaemic episodes, and the fear of such episodes recurring, caused significant disutility. The relevant paragraph states;[12]

"The Committee accepted that episodes of hypoglycaemia are potentially detrimental to an individual's quality of life. This is partly the result of an individual's objective fear of symptomatic hypoglycaemic attacks as indicated in the economic models reviewed in the Assessment Report. In addition, as reported by the experts who attended the appraisal meeting, individuals' quality of life is affected by increased awareness and uncertainty of their daily blood glucose status and their recognition of the need to achieve a balance between the risk of hypoglycaemia and the benefits of longer-term glycaemic control. The Committee understood that improvement in this area of concern regarding the balance between hypoglycaemia and hyperglycaemia could have a significant effect on an individual's quality of life."

However, the guidance did not specify the amount of utility lost because of fear of hypos, and nor did the Technology Assessment Report,[144] because it was based on the industry submission from Aventis, which was classed as confidential. But clearly the utility gain from reducing the fear of hypoglycaemia was enough to change a very large cost per QALY to an affordable one. There is the probability that a reduction in the rate of severe hypoglycaemia events may reduce the fear of severe hypoglycaemia events, though the impact of this seems likely to be variable across patients. The quality of life impact arising from this would be over and above the direct quality of life impact of severe hypoglycaemia events in themselves.

This may fear effect may only apply to a sub-group of patients, but as an illustration of the possible impact of this, the social tariffs derived by Dolan and colleagues[291] suggest that a move from level 2 within the anxiety subscale of EQ-5D to level 1 would be associated with a 0.07 QoL gain. In a similar vein, the coefficients derived by Brazier and colleagues[292] for the SF-6D questionnaire for the consistent model using standard gamble valuations suggest that a movement within the social dimension from health problems interfering moderately to not interfering would be associated with a 0.022 QoL improvement. Similarly, an improvement in the mental health subscale from feeling downhearted some of the time to little or none of the time would be associated with a 0.021 QoL improvement. However, the proportion of patients in whom a reduction in severe hypoglycaemic events would result in these changes to the social dimension or mental dimension is not known.

Currie and colleagues[266] surveyed 1,305 UK patients with type 1 and type 2 diabetes using both the Hypoglycaemia Fear Survey and the EQ-5D. Each severe hypoglycaemic event avoided was associated with a change of 5.9 on the Hypoglycaemia Fear Survey (HFS). Given a further estimate that each unit change on the HFS was associated with an EQ-5D quality of life change of 0.008 this led to an estimated benefit from reduced fear of severe hypoglycaemic events of 0.047 per annual event avoided. This was coupled with a direct utility loss associated with a severe hypoglycaemic event of 0.0016 to yield an overall patient benefit of 0.05 per unit reduction in annual severe hypoglycaemic events.

The 0.05 quality of life increment was adopted by the previous guideline (CG66) in its evaluation of the effects of exenatide. However, at face value this estimate may be quite high. It suggests that a patient with diabetes in less than perfect health and currently experiencing one severe hypoglycaemia event every two years would in effect be willing to sacrifice an annual 11 days survival to avoid this risk. A patient experiencing one severe hypoglycaemic event would be willing to sacrifice an annual three weeks survival to avoid this risk.

The findings of the study by Currie and colleagues[266] have been given considerable weight by industry and NICE. There are weaknesses in it which need to be considered. It involved a first questionnaire survey of 1500 subjects who had received diabetes care in primary care and hospital, and a later another 3,200 who had had hospital admissions or outpatient appointments. The response rate was 31%. The hypoglycaemic events were reported for the three months before the survey, and this could mean that the results only apply to those with recent events, fresh in the memory; 45% were treated with insulin, and about 63% of these had type 2 diabetes.

Bias might arise through the response bias, and through the effect of recent hypoglycaemic episodes. The economists amongst the authors were from industry, and the study was funded by Sanofi-Aventis and Novo Nordisk.

The independent technology assessment team form Sheffield which did the assessment report for NICE, considered that the disutility was over-estimated.

In terms of the cost per severe hypoglycaemic event that requires medical attention, Leese and colleagues[293] coupled TA53 [12] and NHS reference costs, and suggested costs per hypoglycaemia (as shown in Table 44) of:

Table 44: Cost of severe hypoglycaemic events

	Unit cost	% receiving	Weighted	
Glycagon	£20	90%	£18	Glargine TAR
Ambulance	£144	34%	£49	Leese
A&E	£29	7%	£2	Leese & NHS reference costs TA&E
Ambulance and A&E	£173	52%	£90	Leese & NHS reference costs TA&E
Hospital	£631	28%	£176	Leese & NHS reference costs TNELIP
Weighted total			£335	

Note that using the unit costs of Leese and colleagues and indexing to the current year (2008) gives an average of £424. However, only a minority of severe hypoglycaemia events will require medical attention, and the average cost per severe hypoglycaemia event will fall proportionately with the percentage of severe hypoglycaemia events that are attended to by relatives or friends and do not require outside medical assistance. For the base case it will be assumed that 20% of severe hypos require outside medical assistance.

Given these uncertainties, where a difference in severe hypoglycaemic event rates has been demonstrated between two treatments, an exploratory analysis will be performed. This will append quality of life increments within the ranges suggested above to the avoidance of a severe hypoglycaemic event, coupled with a range of possible cost savings per hypoglycaemic event avoided.

In terms of the baseline rate of severe hypoglycaemia events that will be assumed to model any observed differences, within the ScHARR modelling of the cost effectiveness of glargine (TA53)12 the cost per severe hypoglycaemic event was reported as £62 (though note that this was subsequently revised) and the nine year cost of severe hypoglycaemic events of around £175 for both glargine and NPH. This in turn implied an annual incidence of severe hypoglycaemic events of 0.35 per patient year, as drawn from Diabetes Audit and Research in Tayside, Scotland (DARTS) data.[294] This is roughly in line with the rate of severe hypoglycaemic events over 26 weeks reported in Heine and colleagues[53] of 8 events among 549 patients, which converts to an annual rate of 0.3 per patient.

The base case will assume a 0.01 utility gain from the reduced fear associated with an annual severe hypoglycaemic event, while the baseline annual rate will be assumed to be 0.35.

8.2.11 The Impact of Nocturnal Hypoglycaemic Events

The Heine and colleagues[53] and Barnett and colleauges[50] studies reported that exenatide caused fewer nocturnal hypoglycaemic events than glargine. While these are unlikely to significantly affect costs, the GDG was of the opinion that the reduction in nocturnal hypoglycaemia would yield a significant benefit to at least a subset of patients for similar reasons as the reduced fear associated with an annual severe hypoglycaemic event outlined above. In order to address this, an additional literature search was undertaken to identify whether any concrete values for this effect could be identified. Two papers were identified that addressed quality of life and nocturnal hypoglycaemic events Davis and colleagues[295] and Levy and colleagues[296], though the latter was only available as an abstract.

Davis and colleauges administered a postal survey among 3,200 patients with diabetes, both type 1 and type 2 and 897 questionnaires were returned to give a response rate of only 28% 590 patients with type 2 diabetes and 271 with type 1 diabetes. The average EQ-5D score among those with type 2 diabetes experiencing only nocturnal hypoglycaemia events, was marginally better than those experiencing daytime hypoglycaemia events that were defined as either mild or moderate. However, patient numbers falling into the only nocturnal category were small. While this was not reported for the EQ-5D results, within the 361 patients with type 2 diabetes who completed SF-36 only 2 patients were reported as having only nocturnal hypoglycaemia events. Within patients with type 1 diabetes a similar pattern was observed.

Across all respondents the average EQ-5D value was reported as being 0.77 for those experiencing only nocturnal hypoglycaemic events, compared to 0.65 among those whose worst hypoglycaemic event was classified as mild or moderate. Again sample size may have been small with only seven respondents of the 605 respondents within the SF-36 data having only nocturnal hypoglycaemic events.

Note that the results of Davis and colleauges would not be anticipated to uncover any additional quality of life impacts from the fear of nocturnal hypoglycaemia.

The abstract of Levy and colleagues[296] summarises the paper as having undertaken a time trade off exercise among both patients with diabetes (n=50) and patients without diabetes (n=75) to estimate the utility loss associated with hypoglycaemic episodes. The health state descriptors were based upon the Hypoglycaemic Fear Survey. The patients with diabetes apparently reported a disutility from rare hypoglycaemic events of -0.01, from intermittent hypoglycaemic events of -0.05, from frequent hypoglycaemic events of -0.17 and from nocturnal hypoglycaemic events of -0.12. Unfortunately, the abstract was not sufficiently detailed to outline either the severity of the hypoglycaemic events or their frequency and as a consequence is of limited use. In comparison with the other estimates for hypoglycaemic events as outlined above the estimates appear to be quite large.

Given the above, the possible effects of treatments' effects upon nocturnal hypoglycaemic events have not been formally quantified within the economic modelling, though the limited results of Davis and colleagues suggest that on average the impact of nocturnal hypoglycaemia events may be limited. Some of the impact of nocturnal hypoglycaemia on quality of life will in any case be captured via the fear of hypos aspect.

8.3 Results

Within the pairwise comparisons that follow the default will be to present the numerical results for the male patient with a BMI of 30kg/m2, augmenting this with a description of results of the other modelling undertaken. The full set of results for the pairwise comparisons

for the four patients modelled: male with BMI 30kg/m2, female with BMI 30kg/m2, male with BMI 30kg/m2 but excluding the weight changes from the UKPDS Outcomes Model while retaining their effect within the "bolt-ons", male with BMI 35kg/m2 and female with BMI 35kg/m2, can be found in appendix 8.

8.3.1 Comparison 1: exenatide versus glargine

The comparison here is in people failing to achieve satisfactory control on dual therapy with metformin and sulphonylurea, and the options are to start exenatide, with the expectation of needing insulin at a later stage, or to start insulin right away. Because glargine is the market leader in basal insulins in England, we use that as the comparator here. This in effect assumes that glargine is cost-effective, compared to NPH. The cost-effectiveness of glargine and detemir versus NPH is examined later.

No allowance is made for pancreatitis in the modelling, on the grounds that the link is as yet unproven – though even if it is confirmed, the occurrence is probably too rare to have any effect on the modelling.

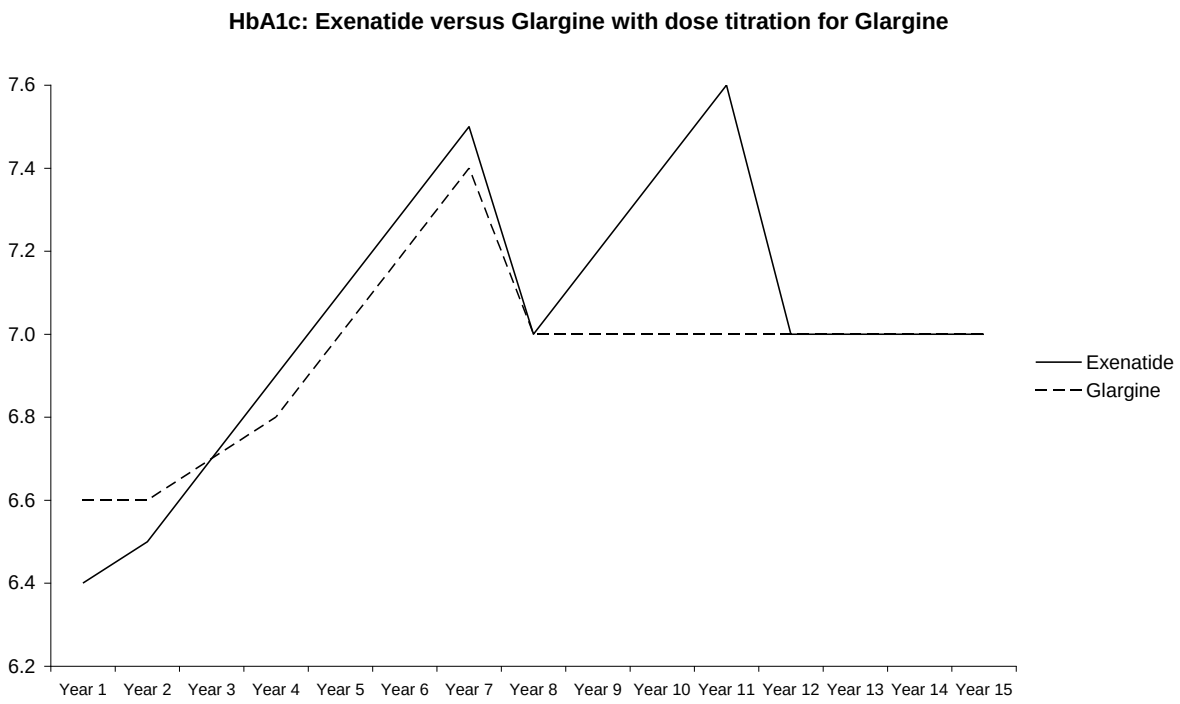
Because the trials were quite short, we lack data on the longer-term relative evolutions of HbA1c on exenatide followed by glargine, and on immediate glargine. There is probably little difference (results were similar in the trials) but differences may emerge over time for reasons given above. One could plausibly speculate that either treatment might have a slight advantage in HbA1c, which however would not be the sole factor in the cost-effectiveness equations, since as will be seen, weight changes also have effects. We therefore give results for both scenarios, to see what happens if evolution of HbA1c is slightly better on immediate glargine (comparison 1a), and then what happens if it is slightly better on exenatide (comparison 1b).

8.3.2 Comparison 1a: evolution of HbA1c assumed to be slower with initial glargine.

The evolution of HbA1c, and the resultant intensifications of therapy once HbA1c rises above 7.5%, has been assumed to follow the path as projected by the UKPDS outcomes model.

As previously noted, glargine has the benefit of possible titration, and when compared to the fixed dose exenatide this may result in a slower worsening of HbA1c through time. So comparing the evolution of HbA1c on glargine and exenatide, we might see the curve for exenatide lying above that for glargine, as shown in Figure 18 (NB that the peaks are exaggerated due to the truncated vertical scale):

Figure 18: HbA1c: Exenatide versus Glargine with dose titration for Glargine



Within the above, for both 1st line exenatide and 1st line glargine there is assumed to be a therapy switch to 2nd line at the start of year 8. Those on 1st line exenatide switch to basal glargine, while those on 1st line basal glargine switch to a basal bolus combination involving glargine. Thereafter, those starting on 1st line exenatide see a further therapy switch to a 3rd line basal bolus combination involving glargine at year 12.

For the base case model of the male patient with a BMI of 30kg/m2 the modelling anticipates the following (see Table 45):

Table 45: Cost per QALY; comparison 1a: exenatide versus glargine: male, BMI 30

Male BMI 30	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8.648	8.638	0.011	8.432	8.422	0.010
Total QALYs	8.617	8.559	0.058	8.402	8.345	0.057
Direct Drug Cost	£9,084	£7,814	£1,271	£8,857	£7,599	£1,257
Total Cost	£19,128	£17,977	£1,151	£19,634	£18,501	£1,133
ICER			£19,854			£19,995

Within this comparison, as before the underlying assumption is that intensification to insulin therapy uses a long-acting insulin analogue rather than NPH, with glargine used here as the current market leader.

The patient impact of treatment with exenatide as compared to treatment with glargine is not large: the UKPDS Outcomes Model suggests an average gain of around 0.01 QALYs. As before, this should be read in conjunction with the section on convergence of the UKPDS Outcomes Model, and represents only a small fraction of the overall lifetime patient QALYs of 1/8th of one percent.

Paralleling this is the relative cost of treatment. The additional lifetime direct drug cost from adopting exenatide prior to glargine of around £1,260 is partially offset by a relatively minor

saving from a reduction in the longer term complications of diabetes to result in an overall net total cost of around £1,140. In the light of this, adopting exenatide prior to glargine is estimated to have a cost effectiveness of between £19,000 and £20,000 per QALY.

Similar results applied for the female patient with a BMI of 30kg/m2, (see Table 46) with a similar absolute gain in QALYs being anticipated, though it should be noted that within the UKPDS Outcomes Model results there is effectively no gain from exenatide, presumably due to the superior weight profile being counterbalanced in effect by the worse HbA1c profile between years 8 and 12. But again, these should be read in conjunction with the section on convergence of the UKPDS Outcomes Model.

Table 46: Cost per QALY: comparison 1a: exenatide versus glargine: female, BMI 30

Female BMI 30	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	9.512	9.511	0.001	9.252	9.250	0.002
Total QALYs	9.476	9.427	0.049	9.218	9.168	0.050
Direct Drug Cost	£9,206	£8,261	£945	£8,970	£8,014	£957
Total Cost	£19,083	£18,181	£902	£19,640	£18,739	£900
ICER			£18,408			£18,005

Despite the greater female life expectancy, the lower absolute patient weight results in the overall net cost falling to around £950, resulting in a slightly better cost effectiveness estimate for the adoption of exenatide prior to glargine of £18,408 per QALY for the no complications modelling and £18,005 per QALY for the with complications modelling.

These results rely upon even smaller estimates of QALY gains than before, and are extremely sensitive to small absolute changes in these. Removing the direct quality of life impact from weight changes from the analysis worsens the anticipated cost effectiveness of exenatide for the male patient with a BMI of 30kg/m2 from £19,854 per QALY to £263,100 per QALY within the no complications modelling, and from £19,995 per QALY to £293,551 per QALY within the with complications modelling.

For the female patient with a BMI of 30kg/m2, removing the direct quality of life impact from weight changes from the analysis results in the gain from exenatide disappearing. A very slight loss is anticipated due to the higher rate of nausea, but the overall effect is so small as to be inconsequential. In this circumstance, glargine would be estimated to be the more cost effective treatment on the basis of its lower direct treatment costs.

As previously noted, the effect of weight changes after intensification from the 1st line treatment cannot be cancelled or changed to those of the 2nd line treatment in the UKPDS Outcomes Model. A sensitivity analysis that assumed no weight changes from treatments within the UKPDS Outcomes Model, but retained the direct quality of life impact of these within the “bolt-ons”, resulted in the following for the male patient with a BMI of 30kg/m2. (see Table 47).

Table 47: Exenatide versus glargine: comparison 1a: male, BMI 30, no weight changes

Male BMI 30	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8.641	8.645	-0.005	8.425	8.429	-0.004
Total QALYs	8.609	8.566	0.043	8.394	8.352	0.042
Direct Drug Cost	£9,079	£7,819	£1,260	£8,852	£7,604	£1,248

Male BMI 30	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
Total Cost	£19,156	£17,937	£1,219	£19,661	£18,465	£1,196
ICER			£28,509			£28,226

The above suggests that despite the better initial HbA1c profile from exenatide, the superior profile of glargine during years 8 to 12 results in a very small anticipated patient loss from the use of exenatide if there are no weight effects entered into the UKPDS Outcomes Model. Despite this, the bolt-on elements to the survival curves are sufficient to still cause exenatide to result in minor patient gains and cost effectiveness estimates of between around £28,200 and £28,500 per QALY. As would be anticipated, removing the direct quality of life impacts from weight gain within this analysis would see exenatide being dominated by glargine.

For the male patient with a BMI of 35kg/m2 the annual net drug cost of treatment with exenatide relative to glargine as compared to the male patient with a BMI of 30kg/m2 is much reduced. This results in the following, as shown in Table 48):

Table 48: Exenatide versus glargine: comparison 1a: male, BMI 35

Male BMI 35	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8.577	8.559	0.018	8.363	8.353	0.010
Total QALYs	8.546	8.481	0.065	8.333	8.276	0.057
Direct Drug Cost	£9,976	£9,745	£231	£9,713	£9,487	£226
Total Cost	£20,180	£20,077	£104	£20,648	£20,559	£89
ICER			£1,602			£1,568

The higher weight and greater dose per kilogram for glargine for the male patient with a BMI of 35kg/m2, coupled with a slight increase in the net QALY gain from exenatide, results in exenatide having an overall lifetime additional direct drug of around £230, though this is offset from increased downstream cost savings to result in an overall net cost of only around £100. While exenatide does not dominate glargine, given the changing net drug costs and that glargine costs are increasing with weight, the adoption of exenatide prior to glargine appears to result in only a small overall cost increase. Patient gains do not have to be large to justify this and provided the direct quality of life impacts from weight changes are realised, the cost effectiveness estimates appear reasonable at around £1,600 per QALY. However, if the direct quality of life impacts from weight changes are not realised, these cost effectiveness estimates worsen to £9,301 per QALY for the no complications modelling and £21,531 per QALY for the with complications modelling.

Given their slightly lesser average weight for a BMI of 35 kg/m2, the results are not as dramatic for the female patient but it remains the case that the net drug costs are much reduced given the greater patient weight (as shown in Table 49).

Table 49: Exenatide versus glargine: comparison 1a: female, BMI 35

Female BMI 35	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	9.452	9.457	-0.005	9.200	9.202	-0.003
Total QALYs	9.417	9.373	0.044	9.165	9.120	0.045
Direct Drug Cost	£10,719	£10,297	£422	£10,421	£9,995	£426
Total Cost	£20,739	£20,434	£306	£21,243	£20,925	£318
ICER			£7,021			£7,034

The additional direct drug cost falls to around £420, with the total net cost being only around £300. Given the direct quality of life gains from weight changes, this results in cost effectiveness estimates of around £7,000 per QALY. However, if these direct quality of life gains from weight changes are not realised, the UKPDS Outcomes Model estimates glargine as being very slightly more effective, and since it is also cheaper than exenatide, it dominates.

8.3.3 Comparison 1b: evolution of HbA1c assumed to be slower with exenatide.

The underlying assumption here is that over the period before the HbA1c lines converge, exenatide gives a small advantage in HbA1c. This gives rise to the results in Table 50.

Table 50: Exenatide versus glargine: comparison 1b: male, BMI 30

Male BMI 30	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8.607	8.538	0.069	8.394	8.331	0.063
Total QALYs	8.567	8.464	0.103	8.354	8.258	0.096
Direct Drug Cost	£8,813	£7,939	£875	£8,592	£7,727	£865
Total Cost	£18,953	£18,258	£696	£19,469	£18,778	£691
ICER			£6,755			£7,180

The quality of life impact of treatment with exenatide as compared to treatment with glargine is not large: the UKPDS Outcomes Model suggests an average gain of between 0.06 and 0.07 QALYs or around ¾ of 1% of the overall lifetime patient QALYs. Due to the superior weight profile from the use of exenatide, the "bolt-ons" increase this gain to around 0.10 QALYs which is a little over 1% of the overall lifetime patient QALYs.

Paralleling this is the relative cost of treatment. The additional lifetime direct drug cost from adopting exenatide prior to glargine of around £900 is partially offset by a relatively minor saving from a reduction in the longer term complications of diabetes to result in an overall net total cost of around £700. In the light of this, adopting exenatide prior to glargine is estimated to have a cost effectiveness of between £6,700 and £7,200 per QALY.

Similar results applied for the female patient with a BMI of 30kg/m2, with a similar absolute gain in QALYs being anticipated. However, given the greater female life expectancy the overall net cost increased to around £1,000 resulting in a slightly worse cost effectiveness estimate for the adoption of exenatide prior to glargine of £7,970 per QALY for the no complications modelling and £8,653 per QALY for the with complications modelling.

These results rely upon relatively small estimates of QALY gains, and as would be anticipated are sensitive to small absolute changes in these. Removing the direct quality of life impact from weight changes from the analysis worsens the anticipated cost effectiveness of exenatide for the male patient with a BMI of 30kg/m2 from £6,755 per QALY to £11,136 per QALY within the no complications modelling, and from £7,180 per QALY to £12,303 per QALY within the with complications modelling. Similarly, for the female patient with a BMI of 30kg/m2, removing the direct quality of life impact from weight changes from the analysis worsens the anticipated cost effectiveness of exenatide from £7,970 per QALY to £13,103 per QALY within the no complications modelling, and from £8,653 per QALY to £15,041 per QALY within the with complications modelling.

Within the UKPDS Outcomes Model, it was noted that the effect of the 1st therapy upon weight could be modelled. But whereas the effect of the switch to the 2nd therapy upon HbA1c could be modelled through the risk input sheets, the effect of the 1st therapy upon weight could not be undone. As a consequence, additional modelling was undertaken that assumed no weight changes from treatments within the UKPDS Outcomes Model but

retained the direct quality of life impact of these within the “bolt-ons” to the resultant estimates from the UKPDS Outcomes Model.

If we assume a slight advantage in HbA1c with exenatide, removing the differential impact upon weight from exenatide relative to glargine within the UKPDS Outcomes Model reduces but does not eliminate the quality of life gain as estimated by the UKPDS Outcomes Model. A gain of around 0.05 QALYs remains, which when coupled with the “bolt-ons” suggests an overall QALY gain to between 0.08 and 0.09 QALYs. The overall net cost also increased slightly due to a smaller net effect upon the complications of diabetes and their associated costs, resulting in a cost effectiveness estimate for the adoption of exenatide prior to glargine of £8,967 per QALY for the no complications modelling and £9,449 per QALY for the with complications modelling.

Whether the estimate of the cost effectiveness for the male patient of between £6,700 and £7,200 per QALY from the application of weight effects within the UKPDS Outcomes model is a more accurate estimate than the £9,000 to £10,000 per QALY when these weight effects are excluded cannot be determined within the modelling, and relates to model structure.

For the male patient with a BMI of 35kg/m2 the annual net drug cost of treatment with exenatide relative to glargine as compared to the male patient with a BMI of 30kg/m2 is much reduced. Similarly, though the life expectancy is shorter for the patient with a BMI of 35kg/m2 this has the effect of slightly increasing the impact of the upfront weight loss on the total lifetime QALYs, given the assumption of the same absolute impact upon patients’ BMI from the use of exenatide and from the use of glargine. As a consequence, modelling results in the following (as shown in Table 51):

Table 51: Exenatide versus glargine: comparison 1b: male, BMI 35

Male BMI 35	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8.533	8.448	0.085	8.328	8.252	0.076
Total QALYs	8.493	8.375	0.118	8.289	8.180	0.109
Direct Drug Cost	£9,958	£9,863	£96	£9,703	£9,612	£91
Total Cost	£20,311	£20,360	-£49	£20,787	£20,844	-£57
ICER	Dominant			Dominant		

The higher weight and greater dose per kilogram for glargine for the male patient with a BMI of 35kg/m2, coupled with a slight increase in the net QALY gain from exenatide, results in exenatide having a small overall lifetime additional direct drug cost of around £100. When coupled with some additional downstream cost savings the modelling suggests that exenatide is slightly cost saving when adopted prior to glargine for the heavier patient. Given this, adopting exenatide prior to glargine is estimated to dominate moving straight to glargine for the male patient with a BMI of 35kg/m2.

This result does not quite carry over to the female patient with a BMI of 35kg/m2, as the absolute effects upon the cost of the glargine containing regimes is slightly less for the female patient as compared to the male patient. When coupled with the slightly better survival curves this leads to an anticipated lifetime total drug cost increase of around £250 for the female patient, though cost offsets reduce the overall additional cost to a little over £100. This is still a relatively marginal cost increase, and results in cost effectiveness estimates of only around £1,000 per QALY from adopting exenatide prior to glargine as compared to moving straight to glargine.

The above comparisons between exenatide and glargine recognise that glargine is the market leader, but in effect assume that glargine is cost effective (relative to NPH). Previous NICE guidance and modelling has typically found glargine to be of poor or borderline cost

effectiveness unless quality of life gains are anticipated from the reduced fear of severe hypoglycaemic events. In the light of this, for comparisons 2 and 3 below the default assumption will be that intensification will lead to the use of NPH insulin.

In summary, taking into account effects, side-effects, costs and expected time to progression, and assuming sufficient weight is lost, exenatide when compared to glargine appears to give ICERs within the range usually regarded as cost-effective for patients with a BMI of 30kg/m2. Provided that the effect of exenatide upon BMI is reasonably consistent across the weight range, the cost effectiveness of exenatide relative to glargine improves as BMI worsens, due in large part to the increasing cost of the required total glargine dose.

8.3.4 Comparison 2: Sitagliptin versus Rosiglitazone

Table 52 shows the first comparison of sitagliptin versus rosiglitazone.

Table 52: Sitagliptin versus rosiglitazone: male, BMI 30

Male BMI 30	No complications			With complications		
	Sitagliptin	Rosiglitazone	Net	Sitagliptin	Rosiglitazone	Net
UKPDS QALYs	8.566	8.549	0.017	8.347	8.342	0.005
Total QALYs	8.479	8.447	0.032	8.263	8.242	0.021
Direct Drug Cost	£5,793	£5,938	-£145	£5,628	£5,779	-£151
Total Cost	£16,083	£16,277	-£194	£16,650	£16,853	-£203
ICER	Dominant			Dominant		

The point estimates above suggests that the very slightly greater improvement in HbA1c from the use of sitagliptin coupled with a superior weight profile results in a small net gain for patients from its use relative to rosiglitazone, as estimated by the UKPDS Outcomes Model. But the absolute gains are so small that despite the 250,000 iterations applied within the modelling, it may be more appropriate to conclude that sitagliptin is clinically equivalent to rosiglitazone, and could even be slightly less effective. However, the patient gain from sitagliptin increases to around 0.02 to 0.03 QALYs with the application of the "bolt-ons" as would be anticipated given the better weight profile, but this remains a relatively small gain of only between ¼ and ⅓ of 1% of the overall lifetime patient QALYs.

The more reliable results, as would be anticipated given the minor differences in treatment effect, are the differences in the direct drug costs. Sitagliptin is somewhat cheaper than rosiglitazone and as a consequence results in an anticipated lifetime direct drug cost saving of around £150 per patient, or around 2.7%. Note that this is the lifetime cost and includes the cost of later NPH insulin therapies which are common to both regimes. While on 1st line therapies the differences in direct drug costs are somewhat larger at 9.4%.

This net direct drug cost saving of around £150 applies with reasonable consistency across the patients modelled. But it should be borne in mind that the glitazones will shortly be coming off patent with the likelihood of significant price reductions as generic formulations become available. Paralleling the difference in the drug costs of the two regimes, a fall of 9% in the price of rosiglitazone would equalise its regimen cost with one containing sitagliptin.

Concerns about the cardiovascular safety of rosiglitazone mean that its use is also declining, which may limit the relevance of this comparison.

8.3.5 Comparison 3: Vildagliptin versus Pioglitazone

Table 53 shows the first comparison of vildagliptin versus pioglitazone.

Table 53: Vildagliptin versus pioglitazone: male, BMI 30

Male BMI 30	No complications			With complications		
	Vildagliptin	Pioglitazone	Net	Vildagliptin	Pioglitazone	Net
UKPDS QALYs	8.561	8.590	-0.029	8.353	8.378	-0.025
Total QALYs	8.468	8.479	-0.011	8.262	8.269	-0.007
Direct Drug Cost	£5,371	£5,824	-£453	£5,220	£5,665	-£445
Total Cost	£15,731	£16,180	-£449	£16,309	£16,756	-£446
ICER			£39,846			£66,799

The pairwise comparison of vildagliptin against pioglitazone is unusual in having the main clinical outcomes pull in opposite directions, though this recurs in the pairwise comparison of detemir and NPH. Vildagliptin has a marginally poorer effect upon HbA1c: -0.88% as compared with -0.98% for pioglitazone, but it has a slightly better weight profile: a gain of only 0.3kg as compared to a gain of 1.9kg for pioglitazone.

Note that in the above, the move from pioglitazone to vildagliptin is anticipated to result in a slight loss of utility while also being coupled with a reduction on overall cost. In this situation, cost effectiveness improves as cost saving increase. For instance, both the no complications and the with complications modelling anticipates roughly the same cost saving of -£450 but the patient loss is greater at -0.011 QALYs within the no complications modelling as compared with -0.007 within the with complications modelling. Both sets of modelling suggest that the cost saving from vildagliptin is warranted as the patient loss is small in both cases, but the case for this is stronger within the with complications modelling.

But the situation is reversed within the modelling of the female patient with a BMI of 30kg/m2 as outlined in Table 54.

Table 54: Vildagliptin versus pioglitazone: female, BMI 30

Female BMI 30	No complications			With complications		
	Vildagliptin	Pioglitazone	Net	Vildagliptin	Pioglitazone	Net
UKPDS QALYs	9.428	9.427	0.000	9.175	9.176	-0.001
Total QALYs	9.328	9.310	0.019	9.078	9.061	0.017
Direct Drug Cost	£5,824	£6,265	-£441	£5,646	£6,082	-£437
Total Cost	£15,959	£16,502	-£543	£16,581	£17,112	-£531
ICER	Dominant					Dominant

The UKPDS Outcomes Model now no longer anticipates any real gain from the use of pioglitazone, and the bolt on effects of the direct quality of life impacts result in a small gain from the use of vildagliptin. Within the UKPDS Outcomes Model it appears that the greater longevity of the female patient in general may lead to the impact of BMI upon CHF having more time to lead to the resultant knock on effects upon the other complications modelled, so causing the superior weight profile of vildagliptin to balance its marginally worse impact upon HbA1c.

This pattern broadly repeats itself for the modelling of patients with a BMI of 35kg/m2, the only notable change within this being that for the male patient while the UKPDS Outcomes Model still projects a vanishingly small loss from the use of vildagliptin, -0.014 QALYs per patient, the bolt-ons are sufficient to turn the overall patient impact into an even smaller gain of 0.04 QALYs per patient.

The reliability of QALY differences of this magnitude is questionable, particularly in the light of the previous discussion as to convergence within the modelling. It may be better to

conclude that there remains uncertainty as to the patient impact of vildagliptin as compared to pioglitazone, with any net effect arising from the impact of changes in weight and HbA1c being likely to be minor. The more reliable result is a fairly consistent reduction in the average direct drug cost of around £450.

As with the comparison of sitagliptin with rosiglitazone, the above will change when pioglitazone comes off patent. A fall of around 22% in the price of pioglitazone would equalise its regime cost with one containing vildagliptin.

In summary, the gliptins and the glitazones appear roughly equivalent in glycaemic effect, but the former have an advantage in avoidance of weight gain, which together with their lower (at present) costs may give them an edge. However, given the size of the QALY estimates and uncertainties around them, it would be inappropriate to say that the glitazones were definitely less cost-effective than the gliptins.

This does not take into account the side-effects of the glitazones. These apply more with rosiglitazone, but pioglitazone also has problems with fractures and heart failure. However, until we have longer follow-up we will not know whether the gliptins have as yet unreported long-term side-effects.

8.3.6 Comparison 4: Glargine versus NPH

Table 55 shows a comparison of glargine versus NPH.

Table 55: Glargine versus NPH: male, BMI 30

Male BMI 30	No complications			With complications		
	Glargine	NPH	Net	Glargine	NPH	Net
UKPDS QALYs	8.538	8.540	-0.002	8.331	8.333	-0.003
Total QALYs	8.464	8.457	0.007	8.258	8.253	0.006
Direct Drug Cost	£7,939	£6,111	£1,828	£7,727	£5,946	£1,780
Total Cost	£18,258	£16,402	£1,855	£18,778	£16,980	£1,798
ICER			£281,349			£320,029

In the base UKPDS Outcomes Model, for the male patient with a BMI of 30kg/m2, there was no difference in QALYs between glargine and NPH. (Indeed one run indicated a very small loss of between -0.002 and -0.003 QALYs when compared with NPH, which given the same effect upon HbA1c and a slightly superior weight profile for glargine, this result appears to have arisen from the convergence issues alluded to previously.)

The bolt-on direct quality of life impacts of the slightly superior weight profile of glargine coupled with its 0.82 relative risk of severe hypoglycaemic events as compared to NPH yield a gain of 0.009 QALYs, to lead to an overall net impact gain of 0.006 to 0.007 QALYs from the use of glargine. This is inconsequential.

The female modelling, again for a BMI of 30kg/m2, shows similar results, though for this the UKPDS Outcome Model results in a gain from glargine of 0.002 QALYs which is again likely to be well within the bounds of modelling variability due to convergence, despite 250,000 iterations. The bolt-on gains are similarly small at 0.008 QALYs to take the overall net gain from the use of glargine to 0.010 QALYs for both the no complications modelling and the with complications modelling. While this reduces the estimate cost effectiveness of glargine to £177,940 per QALY for the no complications modelling, and to £179,074 per QALY for the with complications modelling, these estimates are clearly well outside usual bounds for cost effectiveness.

Among patients with a BMI of 30kg/m2 the clear result is an average net direct drug cost of between £1,800 and £1,900 from the use of glargine.

For patients with a BMI of 35kg/m2 the UKPDS Outcomes model suggests slightly larger gains of between 0.002 and 0.005 QALYs, with the bolt-ons increasing this to between 0.010 and 0.013 QALYs. However, the greater weight and dose per kilogram increase the overall net cost and the estimated cost effectiveness of glargine remains poor at between £189,400 per QALY and £233,187 per QALY.

Among patients with a BMI of 35kg/m2 glargine is estimated to result in a net direct drug cost increase from the use of glargine of around £2,500.

The above calculations do not take account of any differences in mortality from severe hypoglycaemia, which might be expected to run in parallel with e.g. the frequency of nocturnal hypoglycaemia. Such mortality is not easily integrated into the UKPDS model, but data are lacking in any case.

8.3.7 Comparison 5: Detemir versus NPH

Table 56 shows the comparison of detemir versus NPH.

Table 56: Detimir versus NPH: male, BMI 30

Male BMI 30	No complications			With complications		
	Detemir	NPH	Net	Detemir	NPH	Net
UKPDS QALYs	8.530	8.540	-0.010	8.316	8.333	-0.018
Total QALYs	8.472	8.457	0.015	8.259	8.253	0.006
Direct Drug Cost	£8,826	£6,111	£2,715	£8,585	£5,946	£2,638
Total Cost	£19,128	£16,402	£2,726	£19,621	£16,980	£2,641
ICER			£187,726			£417,625

The results for detemir relative to NPH mirror those of glargine relative to NPH outlined above. There is a slight worsening in the anticipated net patient impact from the UKPDS Outcomes Model for detemir. While this might be anticipated given the slightly worse HbA1c profile, the overall effect is small, may have been impacted by the slightly superior weight profile for detemir and may still be subject to a degree of variability due to convergence given the size of the overall impact.

The bolt-ons have a slightly larger effect than in the modelling of glargine relative to NPH, as would be anticipated given that detemir has a superior weight profile and a slightly better relative risk of severe hypoglycaemic events of 0.72. But the net patient impacts remain slight. The resulting estimates of the cost effectiveness of detemir relative to NPH are well outside conventional thresholds.

Note that as in the modelling of glargine relative to NPH for the female patient of BMI 30kg/m2, within the comparison of detemir with NPH the UKPDS Outcomes model again suggests little to no difference in patient impact between the two treatments. The bolt-ons in terms of the direct quality of life impacts from weight changes and severe hypoglycaemic events lead to an anticipated gain of between 0.024 and 0.027 QALYs, but this still results in cost effectiveness estimates of £102,007 per QALY for the no complications modelling and £113,988 for the with complications modelling.

Net costs are somewhat worse for detemir relative to NPH when compared with glargine relative to NPH. This is mainly due to the difference in dosing requirement, the cost per unit being the same. For patients with a BMI of 30kg/m2 the net direct drug cost is anticipated to

be around £2,700 to £2,800, while for patients with a BMI of 35kg/m2 the net direct drug cost is anticipated to be around £3,600 to £3,800.

8.3.8 Caveats

For all the results above the anticipated differences in the QALYs are small given the forty year time horizon. The differences in overall QALYs as outputted from the UKPDS Outcomes model are small. Despite 250,000 iterations, small variations may remain between treatments due to the model not having completely converged. This should be borne in mind since given modelling uncertainties even small reductions in the anticipated QALY differences could give rise to large increases in the cost effectiveness estimates. Also note that although the utility coefficient on patients' BMI is small with a detriment per point of only 0.0061 QALYs, it is sufficient to drive some of the analysis given the small differences in overall QALYs as outputted from the UKPDS Outcomes model.

Given the findings of our review and meta-analyses of the insulins, it is not surprising that the long-acting analogues are not cost-effective compared to NPH. The cost-effectiveness analysis hinges on small differences in weight gain, the poorly-quantified fear of hypoglycaemia, and the baseline BMI and hence daily dose. The price difference is larger and the clinical advantages small.

One caveat is that the results of the meta-analyses are based on averages from trials. Some patients will have more trouble with hypoglycaemia than others, either having more episodes, or having poorer control of glucose levels because of fear of hypos. For them, the utility gain from switching to an analogue may be greater, and hence cost-effectiveness better.

We also heard from members of the GDG, that injection devices for the newer insulins were better. This might also have some effect on quality of life.

A caveat is necessary when comparing detemir with glargine. In the head to head trial by Rosenstock and colleagues[177], detemir was used twice daily in 55% of patients, whereas glargine was used once daily. The total daily doses were 1.0 U/kg with twice daily detemir, 0.52 u/kg with once daily detemir, and 0.44 u/kg with glargine. This would make detemir more expensive. However in the very large PREDICTIVE study, 82% of over 20,000 patients on detemir took it once daily.[270]

The only definite advantage of NPH is cost. (There could be other unknown advantages if the analogues have any as yet undiscovered side-effects.) The cost difference may only be £170 to £230 a year per patient for glargine relative to NPH, though this would increase for very obese patients. However if about 30% of the roughly 2.2 million people with type 2 diabetes in England are treated with insulin, the difference between using NPH and the analogues could be of the order of £100 million to £150 million per annum. This might have to be taken from other forms of diabetes care, such as structured education, or screening for complications.

In summary, as was recommended in the NICE Clinical Guideline CG66, NPH should be preferred as first line insulin, rather than a long-acting analogue. The analogues have modest advantages but at present much higher cost.

In some patients, the benefits of the analogues relative to NPH may be greater, and cost-effectiveness correspondingly better.

8.3.9 The comparator treatments - exploratory indirect comparisons

In an ideal world, we would have direct comparisons of all the competing drugs. Unfortunately, as reported in the clinical effectiveness chapter, there are comparisons for which there are no trials, and others for which evidence is sparse. The most important

example is probably the lack of trials comparing exenatide with the gliptins, since when looking for new third line agents, these are the truly new ones.

NICE therefore asked us to carry out some indirect comparisons. These involve comparing one drug with another through two or more trials against other agents for example using one trial of drug A vs drug B, and another of drug B versus drug C, to compare A and C indirectly. There are various problems in that sort of analysis, such as selection bias. The patients in the trial may have different characteristics which affect the outcomes. These characteristics might have different implications for the different drugs. For example, increases in BMI increase the cost of glargine but not of exenatide. If drug B was exenatide and the patients in one trial are much heavier than in the other, comparing drugs A and C could be misleading.

The problems of indirect comparisons have been reported by Glenny and colleagues[297] who examined the results of 44 analyses in which interventions could be compared both directly and indirectly, and found that;

"There were considerable statistical discrepancies between the direct and indirect estimates, but the direction of such discrepancy was unpredictable. The relative efficacy may be overestimated or underestimated by the indirect comparison…"

The clinical effectiveness section reports the number of drug options for clinicians to consider. For some choices, there is strong evidence from RCTs with direct head to head comparisons. For other choices, there are no direct comparisons at present. In order to examine possible relativities, exploratory indirect comparisons were carried out. These were regarded as hypothesis-generating rather than as firm evidence, and may be a useful way of identifying comparators for future head to head trials. The results were provided to the GDG for discussion purposes but are not included here.

9 Chapter 9 Discussion

The new (and some not so new) drugs are useful additions to the therapeutic armamentarium in diabetes, and our review shows that they are clinically effective. Their cost-effectiveness depends on when they are used, and the comparators. NPH should be the insulin of first use in type 2 diabetes but has now been largely superseded. So the cost-effectiveness of exenatide depends on whether it is compared with what is used (mainly glargine) or what should be used (NPH).

The key questions for their use are where they fit into the treatment pathways, but those are questions for the NICE Guideline Development Group, not for this review.

9.1 Weaknesses in evidence

The main weaknesses are evidence gaps on clinically relevant scenarios, and on long-term safety. For example, there are about 15 trials of the DPP-4 inhibitors against placebo, and almost as many against other drugs as monotherapy, but few with them as third line agents (i.e. added to dual treatment with metformin and a sulphonylurea), and even fewer in head to head comparisons with other potential third line agents.

Most trials are short term, and may not provide any indication of long-term safety issues, such as pancreatitis with exenatide. Only time will tell how often that happens, and whether (if confirmed) it is a problem only with exenatide, or with all GLP-1 agonists.

When comparing drugs, one problem is that the primary effects on glycaemic control are often roughly similar, in that the drugs improve blood glucose control by similar amounts. Comparisons then depend mostly on side-effects such as weight gain or hypoglycaemia, or on quality of life effects, which may be less well-defined or less well-documented than the primary outcome, which is usually HbA1c .

9.2 Compliance

People with type 2 diabetes often have co-morbidities such as hypertension or hyperlipidaemia for which they receive medications. Many should be on a statin to reduce cardiovascular risk; most are overweight. Data from Aberdeen City practices (unpublished) show that from 70% to 91% of people with diabetes are overweight, and that 34% to 53% are obese. Many will have weight-induced osteoarthritis and will be taking medication for that too. So they may be taking several non-diabetic drugs.

The more drugs a patient has to take, the poorer the adherence. Donnan and colleagues from Dundee[298] found that even those on only one glucose lowering agent have poor compliance, with adequate adherence in only one in three. Compliance is better with a single daily dose.[298] Those taking other medications had poorer compliance than those on just a hypoglycaemic agent. In another study from Dundee, Donnelly and colleagues[299] found that adherence to prescribed insulin dose was only 71%. Poorer adherence was associated with poorer control.

Farmer and colleagues[300] carried out a questionnaire survey in Aylesbury. Most of the 121 respondents (all with type 2 diabetes) had positive views about the benefits of taking their medications. In particular, 86% believed that taking them regularly would reduce the chance of them needing insulin treatment. The proportion worried about weight gain was small (13%) and the fear of weight gain did not appear to reduce adherence.

A systematic review of medication adherence by Odegard and colleagues[301] summarises the barriers to taking medicines, and the interventions which may help. Some of the studies are more relevant to the North American situation where people have to pay for drugs, but much

of it is relevant to the UK. The review concurs with the work of Donnan and colleagues (mentioned above), that common barriers to adherence include complexity of regimen and number of doses.

The implication for the treatment of type 2 diabetes may be that we should keep both the number of drugs and the number of tablets or injections per day as low as possible.

9.3 Research needs

The key question is: after metformin and sulphonylurea therapy has failed, what is the most effective and cost-effective next step? And for whom? Different drugs might be better for different subgroups (for example, subgroups based on weight).

We also need more data on some subgroups under-represented in the trials, such as the elderly, ethnic groups, obese children with T2DM, and those with renal impairment.

The main weaknesses in the evidence base at present are;

- The lack of long-term data on the efficacy and safety of exenatide and the gliptins
- We also need long-term data on whether the incretin-based drugs will slow the progression of disease, for example compared to progression rates on insulin
- A lack of trials directly comparing exenatide and the gliptins
- We need more data on combined treatment with insulin and either exenatide or a gliptin.
- Still missing, a UK trial of intensive lifestyle intervention in type 2 patients failing on maximal oral agents, similar to the trial by Aas and colleagues.[27]

At the March 2009 Annual Professional Meeting of Diabetes UK, there was a large batch of abstracts, mainly posters, reporting the results of case series of patients on exenatide. Most had small numbers, and follow-up was usually for only three months. Without control groups, we cannot say how much of the changes were “trial effects”, but many posters reported reductions in HbA1c of more than 1% and in weight of more than 5kg. The few which reported data from more than one time interval showed less impressive changes in HbA1c at six months than at three months, but weight loss continued.

A few posters reported on the use of exenatide in combination with insulin, which as stated earlier in this review, does seem a logical combination with basal insulin targeting fasting and other pre-prandial hyperglycaemia, and exenatide (or other GLP-1 agonist) targetting post-prandial hyperglycaemia. One poster by Vithian and colleagues[302] reported that half of 42 obese type 2 patients previously on insulin could stop that after a mean of 19 weeks on exenatide, and another 29% could reduce the dose by 50%. The fall in HbA1c was 0.75% and in weight, 5%.

Price and colleagues[303] tried exenatide in 10 obses patients on over 100 units of insulin per day, and reported a mean fall in HbA1c of 1.2% and in BMI of 0.7% at 3 months. Median insulin dose per fell fell by 40 units/day, from a median at baseline of 201 unit/day.

Brake and colleagues[304] tried exenatide in a mixed group of 24 patients (some on insulin, some not) and found that amongst those on insulin, HbA1c fell by 1.55% by 3 months and weight by 9.6kg.

So there seems to be sufficient evidence to justify larger trials of the combination of metformin, insulin and GLP-1 agonists.

Future trials are likely to use the long-acting version of exenatide. Its competitor, liraglutide, has already been tested in various trials in the Liraglutide Effect and Action in Diabetes (LEAD) studies[305], but some of these would be exclusions under our criteria. A long-acting form is now in phase 2 studies.

It is unlikely that trials will be big enough or long enough to provide hard endpoints such as complications or mortality; they will provide intermediate outcomes such as HbA1c, BMI, quality of life, hypoglycaemia, postponement of need for insulin, and adherence (the last related to complexity of regimen). Trials should use strict definitions of the different forms of hypoglycaemia.

There may be trade-offs between efficacy and adherence.

We also need more data on the fracture problem with pioglitazone (just pioglitazone because rosiglitazone use is already in decline).

Present evidence on exenatide suggests that there is no long-term preservation of beta cell capacity by a direct effect on the pancreas, but if weight loss continued over years, would that have an indirect effect by reducing insulin resistance?

It would be useful if evidence of beta cell mass could be obtained directly, rather than by waiting for long-term deterioration in glycaemic control (e.g. 9 years as in UKPDS 17). One option might be newer forms of imaging, if these could detect changes, or lack of changes, in only a few years. The methods have been reviewed by Meier.[31]

This review, in line with the NICE guideline, has assumed a step-wise approach in the management of type 2 diabetes, with insulin as a late stage. We note the arguments for earlier use of insulin, but also the reality that in many patients, especially the more overweight, it often does not achieve good control

However, recent research has suggested a radical approach to insulin treatment in type 2 diabetes. Weng and colleagues[306] carried out a randomised trial in newly-diagnosed Chinese people with type 2 diabetes, of intensive insulin therapy (CSII or MDI) or oral agents for short periods, given for a few days (under 8 days in most) to achieve good glucose control, followed by two weeks of maintained normoglycaemia. Drug treatment was then stopped, and patients continued on diet and exercise alone. They were monitored for relapse.

At 12 months, 51% of the CSII group, 45% of the MDI group, and 27% of the OHA group were still in remission. Relapse was defined as fasting PG over 7.0 mmol/l or 2-hour more than 10 mmol/l.

These results suggest that a period of early tight control can produce lasting remission. It is possible that repeated short periods (say once a year) might be worthwhile.

This approach needs to be replicated in other populations. The results might not be applicable to other countries. The Chinese patients had a mean BMI of only 25. There were some weaknesses in the design, such as a weak method of randomisation by sealed envelopes, but the main design flaw was the absence of a diet and exercise alone arm.

The results are in line with a few other smaller studies of intensive therapy in newly diagnosed type 2 diabetes, reviewed by Retnakaran and Drucker in an editorial which accompanied the Lancet article by Weng and colleagues.[307]

9.3.1 Cost-effectiveness studies

The main weakness in the literature is the number of studies funded by the manufacturers, though often carried out by commercial consultancies, which tend to find that their drug is cost-effective, often by being somewhat selective in underlying assumptions.

For assessing cost-effectiveness, we need better data on issues around the effects on quality of life of changes in weight, nocturnal hypoglycaemia, and the fear of hypoglycaemia.

9.3.2 Alternatives to polypharmacy

Lastly, but perhaps most important of all, we need more studies of the type done by Aas and colleagues[27], on intensive lifestyle intervention in people failing on oral agents.

9.4 Recent comments from other reviewers.

The Drug and Therapeutics Bulletin[308] took a fairly firm line on exenatide, sitagliptin and vildagliptin;

"While, on current evidence, we cannot recommend the routine use of these drugs, there may be individual circumstances in which they may be helpful. For example, exenatide may provide a useful alternative to insulin, particularly since it does not seem to cause weight gain. However exenatide frequently causes nausea and vomiting, and it is much more expensive than insulin therapy. There seem to be few convincing reasons for preferring sitagliptin or vildagliptin to other oral hypoglycaemic options"

This seems a little harsh on the gliptins, since they also do not cause weight gain.

The Australian National Prescribing Service[309] concluded that NPH should be the initial basal insulin therapy in type 2 diabetes, mentioning concerns about the long-term safety of glargine and detemir.

One reviewer of the NICE guidelines issued in May 2008 noted the problems when new evidence was continually emerging. In an editorial, Winocour commented[310];

"Sadly, I expect this one will have a very limited shelf life – almost by design-….

An organic web-based document, which is updated annually, could address the need for clinical guidelines where there is a rapidly progressive evidence base."

The shelf-life was expected to be limited because NICE will issue an update early in 2009, which this technology assessment report has been produced to support. However, we know that long-acting exenatide, liraglutide, and two more gliptins will be arriving in the near future, and so the update will soon need updated.

Changes in costs will also change the cost-effectiveness ratios. For example, we would not recommend the use of rosiglitazone at present, because of its cardiovascular safety record and the fact that it has no advantages over pioglitazone or the gliptins. But if the cost of rosiglitazone dropped dramatically (perhaps because generic forms arrived), the equations would change, and we might well recommend rosiglitazone, despite the slightly increased risk, because lower expenditure on oral drugs could release considerable amounts of funds for other investments in diabetes care.

However this illustrates a tension arising from the different perspectives of clinicians, seeking the best treatment for individual patients, and those such as policy-makers or programme managers, who are trying to maximise the health gains which can be achieved with limited resources.

9.5 Conclusion

The new drugs, exenatide, the gliptins and (the not so new) detemir are all clinically effective. Their cost-effectiveness is always relative, and depends on where they are used in the therapeutic pathways.

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10.1 Appendix 1 Search strategies

10.1.1 Appendix 1a. Clinical effectivenesss searches

GLP-1's (exenatide and liraglutide) searches

MEDLINE (Ovid) (1990 – April 2008)

1. exp Glucagon-Like Peptide 1/
2. (Glucagon-Like Peptide 1 or GLP-1).tw.
3. (exenatide or liraglutide).mp.
4. 1 or 2 or 3
5. randomized controlled trial.pt.
6. random$.tw.
7. meta-analysis.pt.
8. review.pt.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to humans
12. limit 11 to yr="1990 - 2008"

Embase (Ovid) (1990-April 2008)

1. exp Glucagon-Like Peptide 1/
2. (Glucagon-Like Peptide 1 or GLP-1).tw.
3. (exenatide or liraglutide).mp.
4. exp Glucagon-Like Peptide 1/
5. meta analysis/ or randomized controlled trial/ or "systematic review"/
6. random$.tw.
7. 1 or 2 or 3 or 4
8. 5 or 6
9. 7 and 8
10. limit 11 to yr="1990 - 2008"

Cochrane Library Issue 2, 2008 (all sections)

(exenatide):ti,ab,kw or (liraglutide):ti,ab,kw or (GLP-1):ti,ab,kw

Science Citation Index and ISI Proceedings (2000-April 2008)

TS=(exenatide or liraglutide) AND PY=(2000-2008)

DocType=Meeting Abstract; Language=All languages; Database=SCI-EXPANDED;

ADA (American Diabetes Association) meeting abstracts

http://scientificsessions.diabetes.org/Abstracts/index.cfm?fuseaction=Locator.SearchAbstracts

EASD (European Association for Study of Diabetes) meeting abstracts

http://www.easd.org/easdwebfiles/annualmeeting/meetingmain.html#past-AM

FDA (U.S. Food and Drug Administration)

http://www.fda.gov/cder/foi/nda/2005/021773_ByettaTOC.htm

EMEA (European Medicines Agency)

http://www.emea.europa.eu/

MHRA (Medicines and Healthcare Products Regulatory Agency)

http://www.mhra.gov.uk/index.htm

Manufacturers' Web sites

Amylin (Exenatide and Exenatide LAR)

http://www.amylin.com/pipeline/byetta.cfm

http://www.byetta.com/index.jsp

http://www.amylin.com/pipeline/exenatidelar.cfm

Novo Nordisk (Liraglutide)

http://www.novonordisk.com/

Contact with Novo Nordisk concerning the unpublished LEAD trials

DPP-4 inhibitors searches

Ovid MEDLINE(R) 1996 to April 2008

EMBASE 1996 to April 2008

1. dipeptidyl peptidase-4 inhibitor$.mp.
2. dipeptidyl peptidase-IV inhibitor$.mp.
3. dpp-iv inhibitor$.mp.
4. dpp-4 inhibitor$.mp.
5. (vildagliptin or sitagliptin or saxagliptin).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6. 1 or 2 or 3 or 4 or 5
7. limit 6 to english language

SCI (meeting abstracts) 2005-2008

dipeptidyl peptidase-4 inhibitor* OR dipeptidyl peptidase-IV inhibitor* OR dpp-iv inhibitor* OR dpp-4 inhibitor* OR vildagliptin or sitagliptin or saxagliptin

Cochrane Library Issue 2, 2008 (all sections)

(dipeptidyl peptidase-4 inhibitor* OR dipeptidyl peptidase-IV inhibitor* OR dpp-iv inhibitor* OR dpp-4 inhibitor* OR vildagliptin or sitagliptin or saxagliptin):ti,ab,kw

ADA (American Diabetes Association) meeting abstracts

http://scientificsessions.diabetes.org/Abstracts/index.cfm?fuseaction=Locator.SearchAbstracts

EASD (European Association for Study of Diabetes) meeting abstracts

http://www.easd.org/easdwebfiles/annualmeeting/meetingmain.html#past-AM

FDA (U.S. Food and Drug Administration)

http://www.fda.gov/cder/foi/nda/2005/021773_ByettaTOC.htm

EMEA (European Medicines Agency)

http://www.emea.europa.eu/

MHRA (Medicines and Healthcare Products Regulatory Agency)

http://www.mhra.gov.uk/index.htm

Insulins - Glargine and detemir searches

Ovid MEDLINE(R) 1996 to April 2008

EMBASE 1996 to April 2008

1. (glargine or detemir).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2. Diabetes Mellitus, Type 2/
3. type 2 diabetes.tw.
4. 2 or 3
5. 1 and 4

Cochrane Library Issue 2, 2008 (all sections)

(glargine or detemir):ti,ab,kw and (type 2 diabetes):ti,ab,kw

ADA (American Diabetes Association) meeting abstracts

http://scientificsessions.diabetes.org/Abstracts/index.cfm?fuseaction=Locator.SearchAbstracts

EASD (European Association for Study of Diabetes) meeting abstracts

http://www.easd.org/easdwebfiles/annualmeeting/meetingmain.html#past-AM

FDA (U.S. Food and Drug Administration)

http://www.fda.gov/cder/foi/nda/2005/021773_ByettaTOC.htm

EMEA (European Medicines Agency)

http://www.emea.europa.eu/

MHRA (Medicines and Healthcare Products Regulatory Agency)

http://www.mhra.gov.uk/index.htm

Manufacturers

Detemir (Levimir) – Novo Nordisk

http://www.novonordisk.com/diabetes/levemir_splash.asp

Glargine (Lantus) – sanofi-aventis

http://www.lantus.com/

Thiazolidinediones (rosiglitazone and pioglitazone) searches

Ovid MEDLINE(R) 1996 to January Week 4 2008

1. exp Thiazolidinediones/
2. rosiglitazone.tw.
3. pioglitazone.tw.
4. 1 or 2 or 3
5. randomized controlled trial.pt.
6. meta-analysis.pt.
7. (random$ or meta-analysis or systematic review).tw.
8. 5 or 6 or 7
9. 4 and 8

Ovid MEDLINE(R) 1996 to January Week 4 2008

1. exp Thiazolidinediones/
2. rosiglitazone.tw.
3. pioglitazone.tw.
4. (risk or safety or adverse or harm or pharmacovigilance).tw.
5. (side-effect$ or precaution$ or warning$ or contraindication$ or contra-indication$).tw.
6. exp Thiazolidinediones/ae [Adverse Effects]
7. 1 or 2 or 3
8. 4 or 5
9. 7 and 8
10. 6 or 9

EMBASE 1996 to 2008 Week 18

1. exp Thiazolidinediones/
2. rosiglitazone.tw.
3. pioglitazone.tw.
4. 1 or 2 or 3
5. (random$ or meta-analysis or systematic review).tw.
6. Randomized Controlled Trial/
7. exp "systematic review"/
8. Meta Analysis/
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to english language

EMBASE 1996 to 2008 Week 18

1. exp Thiazolidinediones/
2. rosiglitazone.tw.
3. pioglitazone.tw.
4. exp Rosiglitazone/ae [Adverse Drug Reaction]
5. exp Pioglitazone/ae [Adverse Drug Reaction]
6. (risk or safety or adverse or harm or pharmacovigilance).tw.
7. (side-effect$ or precaution$ or warning$ or contraindication$ or contra-indication$).tw.
8. 6 or 7
9. 1 or 2 or 3

10. 8 and 9
11. 4 or 5 or 10

Cochrane Library 2008 Issue 2

(thiazolidinedione*):ti,ab,kw or (pioglitazone):ti,ab,kw or (glitazone):ti,ab,kw

Searched web sites below for safety and adverse data information

ADA (American Diabetes Association) meeting abstracts

http://scientificsessions.diabetes.org/Abstracts/index.cfm?fuseaction=Locator.SearchAbstracts

EASD (European Association for Study of Diabetes) meeting abstracts

http://www.easd.org/easdwebfiles/annualmeeting/meetingmain.html#past-AM

FDA (U.S. Food and Drug Administration)

http://www.fda.gov/cder/foi/nda/2005/021773_ByettaTOC.htm

FDA MedWatch

http://www.fda.gov/medwatch/safety.htm

EMEA (European Medicines Agency)

http://www.emea.europa.eu/

MHRA (Medicines and Healthcare Products Regulatory Agency)

http://www.mhra.gov.uk/index.htm

Auto-alerts

Ovid Auto-alerts were set-up for the clinical effectiveness for the rest of 2008 in order to retrieve new studies published after the initial searches (shown above) were run.

10.1.2 Appendix 1b) Economics Searches

GLP-1 economics searches.

Ovid MEDLINE 1996 to May Week 1 2008

1. exp Glucagon-Like Peptides/
2. (Glucagon-Like Peptide 1 or GLP-1).tw.
3. (exenatide or byetta).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4. liraglutide.mp.
5. 1 or 2 or 3 or 4
6. "Costs and Cost Analysis"/
7. "cost of illness"/
8. exp Economics/
9. (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw.
10. exp Health Status/
11. exp health status indicators/
12. exp "Quality of Life"/

13. exp quality-adjusted life years/
14. exp Patient Satisfaction/
15. (qaly$ or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw.
16. (markov or health utilit$ or hrql or hrqol or disabilit$).tw.
17. (quality adj2 life).tw.
18. (decision adj2 model).tw.
19. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 5 and 19
21. from 20 keep 29,38,49
22. from 21 keep 1-3

Total retrieved = 19

Ovid Embase 1996 to 2008 week 19

1. (Glucagon-Like Peptide 1 or GLP-1).tw.
2. (exenatide or byetta).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3. liraglutide.mp.
4. exp Glucagon Like Peptide 1/
5. exp health economics/
6. exp health status/
7. exp "quality of life"/
8. exp patient satisfaction/
9. (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw.
10. (qaly$ or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw.
11. (markov or health utilit$ or hrql or hrqol or disabilit$).tw.
12. (quality adj2 life).tw.
13. (decision adj2 model).tw.
14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 1 or 2 or 3 or 4
16. 14 and 15

Total retrieved = 47

CRD databases (DARE NHE-EED and HTA) April 2008

glp-1 OR liraglutide OR exenatide

Total retrieved = 9

Science Citation Index 1980 – April 2008

Topic=((glp-1 or liraglutide or exenatide) and (cost* or economic* or pharmacoeconomic* or pharmaco-economic*).)

Total retrieved = 19

DPP-IV inhibitors – economics searches

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present (May week 3 2008)

1. dipeptidyl peptidase-4 inhibitor$.mp.
2. dipeptidyl peptidase-IV inhibitor$.mp.
3. Dipeptidyl-Peptidase IV Inhibitors/
4. dpp-iv inhibitor$.mp.
5. dpp-4 inhibitor$.mp.
6. (vildagliptin* or sitagliptin* or saxagliptin*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7. 1 or 2 or 3 or 4 or 5 or 6
8. "Costs and Cost Analysis"/
9. "cost of illness"/
10. exp Economics/
11. (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw.
12. exp Health Status/
13. exp health status indicators/
14. exp "Quality of Life"/
15. exp quality-adjusted life years/
16. exp Patient Satisfaction/
17. (qaly$ or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw.
18. (markov or health utilit$ or hrql or hrqol or disabilit$).tw.
19. (quality adj2 life).tw.
20. (decision adj2 model).tw.
21. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 7 and 21

Total retrieved = 25

Ovid Embase EMBASE 1980 to 2008 Week 22

1. dipeptidyl peptidase-4 inhibitor$.mp.
2. dipeptidyl peptidase-IV inhibitor$.mp.
3. dpp-iv inhibitor$.mp.
4. dpp-4 inhibitor$.mp.
5. (vildagliptin* or sitagliptin* or saxagliptin*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. exp Dipeptidyl Peptidase IV Inhibitor/
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp health economics/
9. exp health status/
10. exp "quality of life"/
11. exp patient satisfaction/
12. (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw.

13. (qaly$ or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw.
14. (markov or health utilit$ or hrql or hrqol or disabilit$).tw.
15. (quality adj2 life).tw.
16. (decision adj2 model).tw.
17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 7 and 17

Total retrieved = 180

NHS-EED May 2008

dipeptidyl peptidase-4 inhibitor* OR dipeptidyl peptidase-IV inhibitor* OR dpp-iv inhibitor* OR dpp-4 inhibitor* OR vildagliptin or sitagliptin or saxagliptin

Total retrieved = 0

SCI database – searched on 2/5/2008.

Topic=((dipeptidyl peptidase-4 inhibitor* OR dipeptidyl peptidase-IV inhibitor* OR dpp-iv inhibitor* OR dpp-4 inhibitor* OR vildagliptin or sitagliptin or saxagliptin) and (cost* or economic* or pharmacoeconomic* or pharmaco-economic* or quality same life or QALY*))

Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI.

Total retrieved = 38

ISI Proceedings

Results Topic=((dipeptidyl peptidase-4 inhibitor* OR dipeptidyl peptidase-IV inhibitor* OR dpp-iv inhibitor* OR dpp-4 inhibitor* OR vildagliptin or sitagliptin or saxagliptin)

and (cost* or economic* or pharmacoeconomic* or pharmaco-economic* or quality same life or QALY*))

Timespan=All Years. Databases=STP.

Total retrieved = 5

Long acting insulin analogues - economics searches

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present (Week 4 April 2008) and EMBASE 1996 to 2008 Week 17

1. (cost* or economic* or pharmacoeconomic* or pharmaco-economic*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2. (quality adj2 life).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. (treatment adj2 satisfaction).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4. (glargine or detemir or levemir or lantus or NPH).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

5. 1 or 3 or 2
6. 4 and 5
7. limit 6 to yr="2005 - 2008"

Total retrieved = 74 from Medline and 294 from Embase

NHS-EED (30 May 2008)

glargine or detemir or levemir or lantus

Total retrieved = 22

SCI database

Topic=((glargine or detemir) and (cost* or economic* or pharmacoeconomic* or pharmaco-economic* or quality same life or satisfaction))

Timespan=2005-2008. Databases=SCI-EXPANDED, SSCI, A&HCI.

Total retrieved =142

Glitazones - economics searches

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present (May week 3 2008)

1. "Costs and Cost Analysis"/
2. "cost of illness"/
3. exp Economics/
4. (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw.
5. exp Health Status/
6. exp health status indicators/
7. exp "Quality of Life"/
8. exp quality-adjusted life years/
9. exp Patient Satisfaction/
10. (qaly$ or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw.
11. (markov or health utilit$ or hrql or hrqol or disabilit$).tw.
12. (quality adj2 life).tw.
13. (decision adj2 model).tw.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. Thiazolidinediones/
16. (Thiazolidinedione$ or pioglitazone$ or rosiglitazone$).tw.
17. 15 or 16
18. 14 and 17

Total retrieved =234

Ovid EMBASE 1996 to 2008 Week 22

1. pioglitazone/ or rosiglitazone/
2. (Thiazolidinedione$ or rosiglitazone$ or pioglitazone$).tw.
3. 1 or 2
4. exp health economics/
5. exp health status/
6. exp "quality of life"/
7. exp patient satisfaction/
8. (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw.
9. (qaly$ or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw.
10. (markov or health utilit$ or hrql or hrqol or disabilit$).tw.
11. (quality adj2 life).tw.
12. (decision adj2 model).tw.
13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 3 and 13

Total retrieved =936

NHS EED (30 May 2008)

thiazolidinedione* or rosiglitazone* or pioglitazone*

Total retrieved=18

Web of Science®

Topic=((thiazolidinedione* or rosiglitazone* or pioglitazone*) and (pharmacoeconomic* or pharmaco-economic* or cost* or economic* or quality same life))

Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI.

Refined by: Document Type=(MEETING ABSTRACT)

Total retrieved=45

10.2 Appendix 2: Characteristics of included trials – GLP-1 receptor agonists

Study	Study Aim	Characteristics of Participants	Number Participants	Study arms	Study Duration
Barnett 2007 [50]	To compare the efficacy and safety profiles of exenatide and insulin glargine in patients with T2DM who had not achieved glycaemic control with a single OAD (MET or an SFU)	T2DM, failing on oral antidiabetics, ≥30 years of age, HbA1c ≥7.1% and ≤11%, BMI >25 kg/m2 and <40 kg/m2	141	1: Exenatide (5 µg bid for 4 weeks then 10 µg bid for 12 weeks) vs 2: Insulin glargine (QD titrated to fasting blood glucose ≤ 5.6 mmol/l) Concurrent medication: Either treatment added to ongoing single oral agent therapy (metformin 56% or sulfonylurea 44%), which was continued at maximal dose.	2 X 16 week treatment periods
Davis 2007 [52]	To explore the safety of substituting exenatide for insulin in patients with T2DM using insulin in combination with oral antidiabetic agents.	Diagnosed with T2D ≥2 years, between 30 and 75yrs; treated with one of following for ≥3mths to 12 yrs: o.d. or b.i.d. NPH insulin; o.d. insulin glargine; o.d. or t.i.d. ultralente insulin or and insulin mixture. All patients on immediate or extended release metformin and/or sulfonylurea for at least 3 mths prior to screening; or fixed dose sulfonylurea/metformin combination therapy. HbA1c level ≤10.5; BMI >27 and <40 kg/m2;	49	1: Exenatide (5 µg bid for 4 weeks then 10 µg bid for 12 weeks) vs 2: Reference group remained on their insulin regimens through 16 week study. Concurrent medication: Patients in both treatment arms continued their oral antidiabetic medications and were instructed to continue their current diet and exercise regimen.	16 weeks
De Fronzo 2005 [65]	To test effects of exenatide on glycaemic control in patients with T2DM failing to achieve glycaemic control with metformin.	T2DM, 19 to 78 years of age, treated with metformin monotherapy, metformin dose >1500mg/day for 3 months before screening, screening FPG of <13.3 mmol/l, BMI 27	336	1: Exenatide (5 µg BID) vs 2. Exenatide (5 µg for 4 weeks then 10 µg for 26 weeks BID) vs 3: Placebo	30 weeks

Study	Study Aim	Characteristics of Participants	Number Participants	Study arms	Study Duration
		to 45 kg/m2, HbA1c 7.1 to 11.0%,.		Concurrent medication: Subjects also continued current regimen of metformin (>1500mg/day)	
Heine 2005 [53]	To compare the effects of exenatide and insulin glargine on glycaemic control patients with T2DM suboptimally controlled with metformin and sulfonylurea	T2DM, 30 to 75 years of age, treated with stable and maximally effective doses of metformin and a sulfonylurea for at least 3 months before screening, HbA1c between 7.0% to 10.0%,BMI between 25 kg/m2 to 45 kg/m2.	551	1: Exenatide (5 ug twice daily for 4 weeks, then 10 ug BID for the remainder of the study) vs 2: Insulin glargine (initial dosage of 10 U/d; then titrated to achieve fasting blood glucose target level of < 5.6 mmol/L) Concurrent medication: Metformin and sulfonylurea doses were fixed at prestudy levels unless patients experienced hypoglycaemia.	26 weeks
Kendall 2005 [58]	To assess effectiveness of Exenatide in achieving glycaemic control in patients with T2DM not adequately controlled with combined metformin-sulfonyl urea therapy	T2DM, age 22-77yrs, screening fasting plasma glucose concentration of <13.3 mmol/l; BMI 27 to 45 kg/m2; HbA1c 7.5 to 11.0%. Metformin dose was ≥1,500 mg/day and sulfonylurea dose at least max effective dose for 3mths before screening.	733	1: Exenatide (5 µg BID) vs 2. Exenatide (5 µg for 4 weeks then 10 µg for 26 weeks BID) vs 3: Placebo Concurrent medication: Also randomised (unblinded) to either maximally effective or minimum recommended doses of sulfonylurea. All subjects continued prestudy metformin regimen.	30 weeks
Nauck 2007 [54]	To compare the safety and efficacy of exenatide with that of biphasic insulin aspart 30/70 in patients with T2DM who were failing	T2DM, age 30 - 75 years, suboptimal glycaemic control despite receiving optimally effective metformin and sulfonylurea therapy for at least 3 months,HbA1c levels ≥7.0	501	1: Exenatide (5 µg BID for 4 weeks and 10 µg BID for the remainder of the study). vs 2: Biphasic insulin aspart 30/70	52 weeks

Study	Study Aim	Characteristics of Participants	Number Participants	Study arms	Study Duration
	to reach treatment goals with optimally effective doses of metformin and a sulfonylurea	and ≤11.0%, BMI ≥25 and ≤40 kg/m2.		Concurrent medication: Patients maintained optimally effective prestudy metformin and sulfonylurea dosages.	
Zinman 2007 [59]	To compare the glycaemic and body weight effects of exenatide versus placebo in patients with T2DM with suboptimal glycaemic control who are receiving a background therapy of TZD or TZD plus metformin.	T2DM, age 21 - 75 years, sub-optimally controlled with TZD (with or without metformin), treated with a stable dosage of a TZD (rosiglitazone, ≥ 4 mg/d, or pioglitazone, ≥30 mg/d) for at least 4 months before screening. Patients received TZD therapy alone or in combination with a stable dosage of metformin (no minimum dosage required) for 30 days. HbA1c value between 7.1% and 10.0% at screening, BMI between 25 kg/m2 and 45 kg/m2.	233	1: Exenatide (5 ug BID for 4 weeks, then 10 µg BID for 12 weeks) vs 2: placebo Concurrent medication: The dosages of TZD and metformin were constant throughout the study.	16 weeks

10.3 Appendix 3: Characteristics of included trials – DPP-4 inhibitors

Study	Methods	Participants	Interventions	Outcomes
Bolli 2008	TRIAL DESIGN: RCT DURATION OF INTERVENTION: 24 weeks DURATION OF FOLLOW-UP: 24 weeks RUN-IN PERIOD: None reported RANDOMISATION PROCEDURE: Not reported BLINDING: Reported as	WHO PARTICIPATED: Patients with type 2 diabetes inadequately controlled with prior metformin monotherapy INCLUSION CRITERIA: 18 to 77 years of age, type 2 diabetes, treated with metformin≥1500mg per day, screening HbA1 7.5-11.0%, non-fertile or using a	INTERVENTION: vildagliptin 100mg daily, two equally divided doses CONTROL: pioglitazone 30mg once daily OTHER TREATMENT: Assumed that participants continued current regimen of metformin.	PRIMARY OUTCOMES: 1. HbA1c *mean HbA1c change from baseline 2. Percentage of patients responsive to treatment (HbA1c<7%, ≤6.5%, reduction ≥1%, ≥0.7%, ≥0.5%, meeting at least one criteria)

Study	Methods	Participants	Interventions	Outcomes
	'double-blind' SETTING: Not clear COUNTRY: Multinational – Germany, UK, USA, Spain, Italy, Switzerland, Austria, South Africa, Australia ITT ANALYSIS? No, per-protocol analysis DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate SAMPLE SIZE CALCULATION: Yes, and adequately powered per-protocol OVERALL RISK OF BIAS: + SOURCE OF FUNDING: Novartis	medically approved birth control method, BMI 22 to 45kg/m2, FPG<15mmol/l EXISTING THERAPY: failing metformin EXCLUSION CRITERIA: History of type 1 diabetes or secondary forms of diabetes, acute metabolic diabetic complications. myocardial infarction. unstable angina or coronary artery bypass surgery within the previous 6 months, congestive heart failure (NYHA I-IV) and liver disease such as cirrhosis or chronic active hepatitis. Also specific abnormal lab. NUMBERS: 576 randomised AGE: Vilda100mg+met 56.3 years SD 9.3 and pio30mg+met 57.0 years SD 9.7 DURATION OF DIABETES: Vilda100mg+met 6.4 years SD 4.9 and pio30mg+met 6.4 years SD 5.2 HbA1c: Vilda100mg+met 8.4% SD 1.0 and pio30mg+met 8.4% SD 0.9 GENDER: Vilda100mg+met 61.7% males and pio30mg+met 64.1% males ETHNIC GROUPS: Vilda100mg+met white 82.4%, hispanic or latino 8.5% asian (non-indian subcontinent) 4.1% black 3.0% others 2.0%		SECONDARY OUTCOMES: 1. FPG 2. Fasting lipids 3. Body weight *Change in body weight (kg) from baseline to 24 weeks Safety

Study	Methods	Participants	Interventions	Outcomes
		pio30mg+met white 81.9%, hispanic or latino 10.3% asian (non-indian subcontinent) 3.9% black 2.5% others 1.4% COMORBIDITIES: not reported COMEDICATIONS: not reported		
Hermansen 2007	TRIAL DESIGN: RCT DURATION OF INTERVENTION: 24 weeks DURATION OF FOLLOW-UP: 24 weeks RUN-IN PERIOD: upto 14 weeks RANDOMISATION PROCEDURE: Not reported but 1:1 BLINDING: Reported a s 'double-blind' SETTING: Not clear COUNTRY: reported as 'multinational' ITT ANALYSIS? Yes, with LOCF DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate SAMPLE SIZE CALCULATION: Yes, but not reported if numbers achieved OVERALL RISK OF BIAS: + SOURCE OF FUNDING: Merck	WHO PARTICIPATED: Patients with type 2 diabetes INCLUSION CRITERIA: 18 to 75 years of age, type 2 diabetes, taking either glimepiride (any dose) alone or in combination with metformin (any dose), or taking another oral hypoglycaemic drug mono-dual-or triple therapy or not taking any oral hypoglycaemic drug during the previous 8 weeks EXISTING THERAPY: If taking glimepiride alone or with metformin, entered placebo run-in. If other regime and depending on HbA1c control, discontinued and started treatment with glimepiride alone or with metformin, dose titrated for 4 weeks, then run-in period 10 weeks, with placebo run-in period if HbA1c ≥7.5% and ≤ 10.5%. Entered for randomization if adherence ≥75% EXCLUSION CRITERIA:	INTERVENTION: sitagliptin 100mg once daily CONTROL: placebo OTHER TREATMENT: Continued stable doses of glimepiride and metformin (as established in the run-in period). Also given rescue therapy of pioglitazone 30mg/day (open label) if FPG not meeting specific, and progressively lower goals after randomization. Discontinued from study if rescue therapy for more than 4 weeks and FPG still high. NOTE: Only reported details for relevant comparator arms	PRIMARY OUTCOMES: 1. HbA1c *mean HbA1c change from baseline. If significant then assessed treatment effects by strata SECONDARY OUTCOMES: 1. FPG 2. Fasting lipids – TC, LDL-C, TG, HDL-C 3. Beta cell function 4. Changes in insulin resistance Safety and tolerability

Study	Methods	Participants	Interventions	Outcomes
		History of type 1 diabetes, treated with insulin in prior 8 weeks, renal dysfunction, history of hypersensitivity, intolerance or contraindications to glimepiride, sulphonylureas, metformin or pioglitazone. NUMBERS: 441 randomised - sit100mg+MET+SU 116 placebo+MET+SU 113 AGE: sit100mg+MET+SU 56.5 years SD 9.6 and placebo+MET+SU 57.7 years SD 8.9 DURATION OF DIABETES: sit100mg+MET+SU 9.3 years SD 5.7 and placebo+MET+SU 10.6 years SD 6.8 HbA1c: sit100mg+MET+SU 8.27% SD 0.73 and placebo+MET+SU 8.26% SD 0.68 GENDER: sit100mg+MET+SU 52.6% males and placebo+MET+SU 59% males ETHNIC GROUPS: sit100mg+MET+SU white 64.7%, black 6.6% hispanic 24.5% asian 5.7% others 5.7% placebo+MET+SU white 71.7%, black 8.0% hispanic 6.2% asian 11.5% others 2.7% COMORBIDITIES: not reported COMEDICATIONS: not reported		

Study	Methods	Participants	Interventions	Outcomes
Nauck 2007	TRIAL DESIGN: RCT DURATION OF INTERVENTION: 52 weeks DURATION OF FOLLOW-UP: 52 weeks RUN-IN PERIOD: 2 week single-blind PLACEBO RANDOMISATION PROCEDURE: Not reported, 1:1 ratio BLINDING: Double blinded. Except for lead-in period (single blind) SETTING: Not clear COUNTRY: Described as 'multinational' ITT ANALYSIS? Per-protocol and all-patients treated analysis DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate SAMPLE SIZE CALCULATION: Not reported OVERALL RISK OF BIAS: - SOURCE OF FUNDING: Merck	WHO PARTICIPATED: Patients with type 2 with inadequate control on metformin INCLUSION CRITERIA: 18-78 years of age, type 2 diabetes, treated with metformin (eligible if not taking any oral therapy, any oral therapy as monotherapy, any oral therapy with metformin, then titrated to METFORMIN monotherapy over 8 week period) EXISTING THERAPY: failing metformin EXCLUSION CRITERIA: History of type 1 diabetes, insulin use within 8 weeks of screening, renal function impairment inconsistent with use of metformin, FPG at or prior to randomization>15.0mmol/l NUMBERS: 1172 randomised AGE: SIT+MET 56.8 (SD9.3) and SU+MET 56.6 (SD9.8) years DURATION OF DIABETES: SIT+MET 6.5 years (SD6.1) and SU+MET 6.2years (SD5.4) HbA1c: SIT+MET 7.7 (SD0.9)and SU+MET 7.6 (SD0.9) GENDER: SIT+MET 57.1% males SU+MET 61.3% ETHNIC GROUPS: SIT+MET	INTERVENTION: sitagliptin 100mg once daily CONTROL: glipizide, initial dose of 5mg with uptitration according to protocol specifications to max of 20mg/day OTHER TREATMENT: Assumed that all participants continued stable regimen of metformin.	PRIMARY OUTCOMES: 1. HbA1c *mean HbA1c change from baseline SECONDARY OUTCOMES: 1. HbA1c *Number (%) of patients achieving HbA1c equal to or less than 7% or 6.5% Change in HbA1c stratified by baseline A1c Safety and tolerability Adverse experiences, lab safety parameters, body weight, vital signs, ECG data Compliance tablet count

Study	Methods	Participants	Interventions	Outcomes
		white 73.5%, black 7.0%, hispanic 7.3%, asian 8.5%, other 3.7% SU+MET white 74.3%, black 6.0%, hispanic 739%, asian 8.4%, other 3.4% COMORBIDITIES: Not reported COMEDICATIONS: Allowed lipid lowering, antihypertensive, thyroid, medications and HRT, birth control – but expected to remain at stable doses. Other treatments for hyperglycaemia not allowed. PHARMACONAIIVE: SIT+MET 4.3% and SU+MET 4.8% at screening		
Scott 2007	TRIAL DESIGN: RCT DURATION OF INTERVENTION: 18 weeks DURATION OF FOLLOW-UP: 18 weeks RUN-IN PERIOD: 2 week single-blind PLACEBO RANDOMISATION PROCEDURE: Not reported, 1:1:1 ratio BLINDING: Double blinded. Except for lead-in period (single blind) SETTING: Not clear COUNTRY: Described as 'multinational' ITT ANALYSIS? All patients treated analysis DESCRIPTION OF WITHDRAWALS AND	WHO PARTICIPATED: Patients with type 2 diabetes treated with metformin INCLUSION CRITERIA: 18 to 75 years of age, type 2 diabetes, treated with metformin at stable dose of at least 1500mg/day for at least 10 weeks prior to screening, HbA1c 7 to 11% EXISTING THERAPY: failing metformin EXCLUSION CRITERIA: Type 1 diabetes, insulin use within 8 weeks of screening, impaired renal function, contraindications for TZDs or metformin. NUMBERS: 273 randomised AGE: SIT100 55.2 years SD	INTERVENTION: sitagliptin 100mg once daily INTERVENTION: rosiglitazone 8,g once daily CONTROL: Placebo once daily OTHER TREATMENT: All participants continued current regimen of metformin. All patients received counseling on exercise and a weight maintaining diet	PRIMARY OUTCOMES: 1. HbA1c *mean HbA1c change from baseline 2. Beta-cell function Proinsulin/insulin ratio and HOMA-beta 3. Meal tolerance test SECONDARY OUTCOMES: 1. Adverse experiences 2. Physical examinations 3. Vital signs 4. Body weight

Study	Methods	Participants	Interventions	Outcomes
	LOSSES TO FOLLOW-UP: Adequate SAMPLE SIZE CALCULATION: Not reported OVERALL RISK OF BIAS: + SOURCE OF FUNDING: Merck	9.8 and ROSI8 54.8 years SD 10.5 and PLACEBO 55.3 years SD 9.3 DURATION OF DIABETES: SIT100 4.9 years SD 3.5 and ROSI8 4.6 years SD 4.0 and PLACEBO 5.4 years SD 3.7 HbA1c: SIT100 7.8 SD 1.0 and ROSI8 737 SD 0.8 and PLACEBO 7.7 SD 0.9 GENDER: SIT100 55% males ROSI8 63% males and PLACEBO 59% males ETHNIC GROUPS: SIT100 caucasian 61%, asian 38%, others 1% ROSI8 caucasian 59%, asian 38%, others 3% PLACEBO caucasian 61%, asian 39%, others 0% COMORBIDITIES: 59% hypertension, 42% hyperlididaemia/dyslipidaemia COMEDICATIONS: Not reported PHARMACONAIIVE:N/A		

10.4 Appendix 4: Characteristics of included reviews - long acting insulin analogues

Review	Inclusion criteria and methodology	Included studies	Quality
Duckworth 2007 [140] focus: clinical evidence for insulin glargine versus NPH insulin funding: industrial (Sanofi-Aventis	INCLUSION CRITERIA study design: not specified participants: patients with type 2 diabetes interventions: insulin glargine versus NPH insulin outcomes: HbA1c, FPG, incidence of	number of included trials: 8 number of participants: 3379 (range 100 to 756) TRIALS: design: all open-label randomised controlled trials	• appropriate and clearly focused question: adequately addressed • in/exclusion criteria described: poorly addressed • literature search sufficiently rigorous to identify all relevant studies: poorly addressed

Review	Inclusion criteria and methodology	Included studies	Quality
USA)	hypoglycaemia, other safety assessments METHODOLOGY search strategy: Pubmed 1996 to 2005; search terms reported; English language only study selection: not described quality assessment: not described data extraction: not described meta-analysis: no data analysis: not described subgroups / sensitivity analyses: none	duration: 4 weeks to 1 year quality: not reported origin: not reported funding: many of the included trials supported by Sanofi-Aventis (no further details) PARTICIPANTS: age: not reported gender: not reported BMI: not reported diabetes duration: not reported HbA1c: mean 8.5 to 9.7% previous medication: see below, some limited details given INTERVENTIONS: 2 trials in patients with previous insulin therapy; 5 trials in insulin-naïve patients on oral therapy; 1 trial included patients on oral therapy plus insulin; dose titration targets 80 to 140 mg/dL (4.5 to 7.8 mmol/L) in 2 trials, 72 to 126 mg/dL (4 to 7 mmol/L) in 1 trial, 120 mg/dL (6.7 mmol/L) in 2 trials, ≤100 mg/dL (5.6 mmol/L) in 3 trials; in trials with previous oral agents: 4 trials continued existing oral therapy, in 1 trial existing oral therapy was replaced by 3 mg glimepiride, in 1 trial fixed dose of 2 g metformin OUTCOMES: HbA1c, FPG, hypoglycaemia, safety, % reaching target HbA1c/FBG	• study selection described: not reported • data extraction described: not reported • study quality assessed and taken into account: not reported • study flow shown: not reported • study characteristics of individual studies described: adequately addressed • quality of individual studies given: not reported • results of individual studies shown: adequately addressed • enough similarities between studies selected to make combining them reasonable: not applicable how well was study done to minimise bias: (-) what is the likely direction in which bias might affect study results? less effect than reported
Horvath 2007 [141] focus: effects of long-term treatment with long-acting insulin analogues (insulin glargine and	INCLUSION CRITERIA study design: randomised controlled trials with parallel or cross-over design, blinded or open-label, with a duration of 24 weeks or longer	number of included trials: 7 RCTs insulin glargine versus NPH (6 analysed, see below), 2 RCTs insulin detemir versus NPH number of participants: (in analysed	• appropriate and clearly focused question: well covered • in/exclusion criteria described: well covered • literature search sufficiently

Review	Inclusion criteria and methodology	Included studies	Quality
insulin detemir) compared to NPH insulin in patients with type 2 diabetes mellitus funding: non-industrial	participants: patients with type 2 diabetes interventions: long-acting insulin analgues (glargine or detemir) versus NPH insulin; in case of combination with oral agents, the antihyperglycaemic agent had to be part of each treatment arm; subcutaneous applications for insulin only outcomes: primary: overall, severe and nocturnal hypoglycaemia; glycaemic control (HbA1c); secondary: mortality, cardiovascular morbidity, diabetic late complications, quality of life, adverse events, costs. METHODOLOGY search strategy: databases searched: Cochrane Library, Medline, Embase, CRD Databases; electronic search strategy shown; citation searches of included trials and reviews; additional internet searches listed; information on unpublished trials sought from Sanofi-Aventis and Novo Nordisk. study selection: two reviewers independently screened titles and abstracts; full articles obtained for citations that appeared to fulfil the inclusion criteria (or in case of disagreement); if disagreement persisted, resolved by a third party. quality assessment: independent assessment of quality by two reviewers; differences in opinion	trials) 3151 for glargine trials (range 110 to 764), 980 for for detemir trials (505 and 475) TRIALS: design: all studies were parallel trials; 2 had a superiority design, 1 and equivalence and 2 a non-inferiority design; in none of the trials participants or caregivers were blinded duration: 6 to 12 months quality: all studies rated as being of insufficient methodological quality (rating C); reporting of randomisation poor in most trials, adequate allocation concealment in 5 trials; discontinuation rates 1.6 to 10.2%; all main analyses used ITT approach origin: 4 trials Europe, 2 North America, 1 Europe and South Africa, 1 Latin America funding: 5 trials were commercially funded, unclear for the rest PARTICIPANTS age: mean age 55 to 62 years gender: numbers given but partially unclear if they refer to men or women, distribution looks balanced BMI: mean 27 to 33 kg/m2 diabetes duration: mean 8 to 14 years HbA1c: mean 7.9 to 9.5% previous medication: no details, none of the trials was performed with pharmaco-naïve patients (i.e. controlled on diet/exercise only) INTERVENTIONS: 6 studies used combinations with oral anti-diabetic	rigorous to identify all relevant studies: well covered • study selection described: well covered • data extraction described: well covered • study quality assessed and taken into account: well covered • study flow shown: well covered • study characteristics of individual studies described: well covered • quality of individual studies given: well covered • results of individual studies shown: well covered • enough similarities between studies selected to make combining them reasonable: well covered how well was study done to minimise bias: (++) what is the likely direction in which bias might affect study results? no likely bias

Review	Inclusion criteria and methodology	Included studies	Quality
	resolved by discussion with a third reviewer; quality parameters assessed: randomisation, allocation concealment, blinding, description of withdrawals and drop-outs, ITT analysis, blinding of outcome assessors data extraction: done independently by two reviewers using data extraction sheets; differences in data extraction resolved by consensus; information extracted listed meta-analysis: yes data analysis: weighted mean differences or odds ratios calculated, random effects model used; heterogeneity assessed using chi-squared test subgroups / sensitivity analyses: planned but not carried out	drugs (5 glargine and 1 detemir), 2 with a short-acting insulin (1 glargine and 1 detemir), and 1 with both (detemir); 1 study required an upward titration of insulin glargine with a target of a fraction of 50% of the basal insulin requirement while the fraction of NPH on the total insulin requirement was left unchanged, thus introducing a difference in the treatments, and the study was therefore not considered further; 1 study compared morning or evening glargine with evening NPH, in all other studies glargine or NPH were injected at bedtime (1 study choice of bedtime or twice daily); two studies (glargine) changed from previous oral antihyperglycaemic treatment to glimepiride during run-in OUTCOMES: glycaemic control (HbA1c), hypoglycaemia, FBG, blood glucose profiles, % reaching target HbA1c, insulin doses, weight change, adverse events	
Tran 2007 [142] focus: clinical and cost-effectiveness of long-acting insulin analogues (insulin glargine and insulin detemir) for the treatment of diabetes melitus (both type 1 and 2) funding: Canadian Agency for Drugs and Technology in Health	INCLUSION CRITERIA study design: randomised controlled trials participants: patients with diabetes mellitus (type 1, type 2 or gestational – only type 2 considered here) interventions: long-acting insulin analogues (insulin glargine or detemir) versus conventional human insulin or oral anti-diabetic agents outcomes: glycaemic control (blood glucose, HbA1c), quality of life,	number of included trials: 9 RCTs insulin glargine, 2 RCTs insulin detemir (type 2 diabetes) number of participants: 4729 (range 110 to 756) TRIALS: design: all open-label parallel trials; 10 full publications, 2 abstracts/posters; most studies described as multi-centre duration: 4 to 52 weeks quality: for full reports, mean Jadad score 2.4 SD0.7, allocation	• appropriate and clearly focused question: well covered • in/exclusion criteria described: well covered • literature search sufficiently rigorous to identify all relevant studies: well covered • study selection described: well covered • data extraction described: adequately addressed • study quality assessed and taken

Review	Inclusion criteria and methodology	Included studies	Quality
	hypoglycaemic episodes, adverse events, complications of diabetes, mortality. METHODOLOGY search strategy: databases searched: Medline, BIOSIS Previews, Pascal, Embase, Pubmed, Cochrane Database of Systematic Reviews from 1990 onwards; electronic search strategy given; alert searches; grey literature obtained by searching listed web sites; manufacturers were asked to provide relevant information. study selection: two reviewers independently selected trials for inclusion; differences in decision resolved by consensus. quality assessment: Jadad scale; allocation concealment, blinding of assessors, intention-to-treat analysis. data extraction: one reviewer extracted data into a structured form, another reviewer checked the extraction. meta-analysis: yes data analysis: fixed and random effects models; heterogeneity assessed using Higgins' I2 value; weighted mean differences, relative risks and risk differences computed. subgroups / sensitivity analyses: none	concealment adequate in 4 studies (unclear in remainder), 90% reported ITT analysis origin: 4 trials Europe, 4 trials North America, 2 trials Europe and South Africa, 1 trial international funding: industrial (where reported) PARTICIPANTS age: mean 53 to 61 years (where reported) gender: 36 to 49% female (where reported) BMI: mean 27 to 35 kg/m2 diabetes duration: mean 8.5 to 13.8 years (where reported) HbA1c: mean 8.4 to 9.8% previous medication: see below INTERVENTIONS: 7 studies including various combinations of oral anti-hyperglycaemic medications, 1 study morning versus evening glargine versus evening NPH, 1 study combination with insulin aspart OUTCOMES: no specific details given, results reported for: glycaemic control, 8-point glucose profiles, hypoglycaemia, adverse events, mortality, quality of life	into account: well covered • study flow shown: well covered • study characteristics of individual studies described: well covered • quality of individual studies given: well covered • results of individual studies shown: well covered • enough similarities between studies selected to make combining them reasonable: yes how well was study done to minimise bias: (++) what is the likely direction in which bias might affect study results? no likely bias
Warren 2004 [144]	INCLUSION CRITERIA study design: methodology including at least one of: a) systematic review,	number of included trials: 5 RCTs for type 2 diabetes number of participants: 1399 (range	• appropriate and clearly focused question: well covered • in/exclusion criteria described: well

Review	Inclusion criteria and methodology	Included studies	Quality
focus: clinical and cost-effectiveness of insulin glargine in its licensed basal-bolus indication (both type 1 and type 2 diabetes) funding: NICE, UK	b) RCT, c) economic evaluations; study duration at least 4 weeks participants: patients with type 1 or type 2 diabetes, requiring insulin for glycaemic control (only type 2 considered here) interventions: insulin glargine versus other long-acting basal insulin outcomes: glycaemic control (blood glucose, HbA1c); incidence and severity of hypoglycaemic episodes METHODOLOGY search strategy: databases searched: Biological Abstracts, CINAHL, Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, EBM Reviews, Embase, HTA Database, Medline, NHS Economic Evaluations Database, OHE Health Economic Evaluations Database, PreMedline, Science Citation Index, Social Sciences Citation Index; electronic search strategies given; searching of reference lists of relevant publications; 45 health services research related resources searched via the internet (list given); citation searches of key papers; no date, language, study or publication type restrictions; list provided by Aventis of peer-reviewed articles of glargine primary research. study selection: titles and abstracts	100 to 518) TRIALS: design: all prospective, 3 clearly described as RCTs, none double-blind, design not clearly documented for 2 trials; 2 full publications, 3 abstracts; most studies described as multi-centre duration: 4 to 52 weeks quality: assessment only possible for 2 articles reported in full; both scored 2 (of 3) on Jadad scale; blinding of patients not possible; none of the studies specified blinded outcome assessment origin: 1 trial Europe, 4 trials USA funding: not reported PARTICIPANTS: age: ~ 59 years (where reported) gender: 47 to 38% female (where reported) BMI: mean 29 to 31 kg/m2 (where reported) diabetes duration: 10 to 14 years (where reported) HbA1c: mean 8.5 to 9.1% (where reported) previous medication: see below, no details INTERVENTIONS: 2 studies of 2 formulations of insulin glargine compared to each other and to NPH, 3 studies of glargine compared to NPH; 2 studies of patients previously on insulin; 3 studies of patients previously on oral medication (and continuing oral medication); insulin doses individually	covered • literature search sufficiently rigorous to identify all relevant studies: well covered • study selection described: adequately addressed • data extraction described: not adequately addressed • study quality assessed and taken into account: well covered • study flow shown: poorly addressed • study characteristics of individual studies described: well covered • quality of individual studies given: well covered • results of individual studies shown: well covered • enough similarities between studies selected to make combining them reasonable: not applicable how well was study done to minimise bias: (+) what is the likely direction in which bias might affect study results? no likely bias

Review	Inclusion criteria and methodology	Included studies	Quality
	screened; full copies of primary research reports, reviews and abstracts obtained; no further details. quality assessment: Jadad scale; blinding of outcome assessment data extraction: done by one reviewer using customised data extraction sheets meta-analysis: no data analysis: text and tables subgroups / sensitivity analyses: none	titrated to achieve target FBG levels; titration periods of varying durations OUTCOMES: glycaemic control, hypoglycaemia, FBG, diurnal blood glucose, % reaching target FBG	
Wang 2003 [143] focus: efficacy and tolerability of insulin glargine funding: not reported	INCLUSION CRITERIA study design: clinical trials, ≥100 participants; includes pharmacodynamic studies, only clinical efficacy trials considered here participants: type 1 or type 2 diabetes, only type 2 diabetes considered here interventions: insulin glargine (no details) outcomes: HbA1c, fasting plasma glucose (FPG), fasting blood glucose (FBG), incidence of hypoglycaemia, measures of tolerability METHODOLOGY search strategy: Medline / Pubmed, Embase (1966 to 2002), Premedline (Nov 2002); search words given; searching of reference lists of relevant publications study selection: not described quality assessment: not described data extraction: not described	number of included trials: 7 RCTs for efficacy, 1 RCT for quality of life number of participants: 2856 (range 100 to 756) TRIALS: design: all trials multi-centre, open-label, randomised trials duration: 4 to 52 weeks quality: inconsistent reporting of mean or adjusted mean changes in primary and secondary efficacy endpoints within and between treatment groups; studies were typically statistically underpowered (only 3 studies included power analysis); 5 studies only available in abstract form origin: Europe and USA funding: unclear, some industrial, indicated that for most studies authors may have had conflicts of interest PARTICIPANTS: age: ~ 59 years gender: not reported BMI: only reported for 2 studies, mean	• appropriate and clearly focused question: adequately addressed • in/exclusion criteria described: poorly addressed • literature search sufficiently rigorous to identify all relevant studies: adequately addressed • study selection described: not reported • data extraction described: not reported • study quality assessed and taken into account: poorly addressed • study flow shown: not reported • study characteristics of individual studies described: adequately addressed • quality of individual studies given: poorly addressed • results of individual studies shown: adequately addressed • enough similarities between studies selected to make

Review	Inclusion criteria and methodology	Included studies	Quality
	meta-analysis: no data analysis: not described subgroups / sensitivity analyses: none	29 to 32 kg/m2 diabetes duration: not reported HbA1c: mean 8.4 to 9.0% (where reported) previous medication: see below, no details INTERVENTIONS: insulin doses individually titrated to achieve target FBG level of ≤120 mg/dL (6.7 mmol/L) (≤100 mg/dL in Fritsche 2002 and Riddle 2002); 2 trials comparing 2 formulations of insulin glargine (containing 30 or 80 µg/mL of zinc); 3 trials of patients not receiving oral anti-diabetic drugs with previous once or twice daily NPH insulin with or without short-acting insulin for post-prandial control; 4 studies comparing once daily insulin glargine with once daily NPH insulin in previously insulin-naïve patients also taking oral anti-diabetic agents OUTCOMES: HbA1c, FPG, self-monitored FBG levels, incidence of hypoglycaemia	combining them reasonable: not applicable how well was study done to minimise bias: (-) what is the likely direction in which bias might affect study results? less effect than reported

10.5 Appendix 5: Characteristics of included trials - long acting insulin analogues

Study	Design	Participants	Interventions	Outcome measures
insulin-naïve, oral antihyperglycaemics – glargine versus NPH insulin				
Pan 2007 (LEAD study)[179] China, France, Korea	**focus**: effect of insulin glargine versus NPH insulin on metabolic control and safety in Asian	**total number**: 443 **N glargine**: 220; 198 completed the trial **N NPH: 223**; 201 completed the trial inclusion criteria: insulin-naïve; Asian; aged ≥40 and	**glargine**: insulin glargine once daily at bedtime (21-23 h), once daily glimepiride (3 mg) in the morning (7-9 h)	**primary**: change in HbA1c level from baseline to endpoint **HbA1c**: HbA1c, proportion of patients with

Study	Design	Participants	Interventions	Outcome measures
	patients with type 2 diabetes, inadequately controlled on oral antihyperglyceamic agents **design**: non-inferiority study; open-label, parallel group randomised trial **multi-centre** **duration**: 24 weeks **follow-up**: no post-intervention follow-up **setting**: **funding**: Sanofi-Aventis Korea	≤80 years; type 2 diabetes according to WHO criteria plus specified blood glucose criteria; poorly controlled on oral hypoglycaemic agents for ≥3 months before study entry; BMI 20-35 kg/m2; HbA1c ≥7.5 and ≤10.5%, fasting blood glucose levels >120 mg/dL (>6.7 mmol/L) **exclusion criteria**: pregnancy; history of ketoacidosis; likelihood of requiring treatment with drugs prohibited by the protocol (e.g. non-selective beta-blockers, systemic corticosteroids) **age**: glargine: 55.6 SD8.4 years; NPH: 56.6 SD8.7 years **gender**: glargine: 59.6% female; NPH: 55.6% female **BMI**: glargine: 24.8 SD3.1 kg/m2; NPH: 25.1 SD3.3 kg/m2 **ethnicity**: n=126 China, 26 Hong Kong, 19 Indonesia, 112 South Korea, 16 Malaysia, 36 Pakistan, 24 Philippines, 32 Taiwan, 48 Thailand, 4 Singapore **diabetes duration**: glargine: 10.3 SD6.3 years; NPH: 10.0 SD5.4 years **previous medication**: not reported, duration of treatment with oral antihyperglycaemic agents: **glargine**: 9.1 SD6.0 years; NPH: 8.6 SD5.2 years **comorbidities**: not reported **subgroups**: none	**NPH**: NPH insulin once daily at bedtime (21-23 h), once daily glimepiride (3 mg) in the morning (7-9 h) **both**: insulin glargine / NPH insulin titrated to a target FBG ≤120 mg/dL (≤6.7 mmol/L), starting at insulin dose of 0.15 U/kg/day **co-interventions**: none **adherence assessment**: no **screening phase**: 3-4 weeks, oral treatments standardised to 3 mg glimepiride, patients were given training in self-administration of insulin and self-monitoring of blood glucose levels	HbA1c <7.5%, proportion of combined responders (both HbA1c <7.5% and FBG levels ≤120 mg/dL) **hypoglycaemia**: proportion of patients with hypoglycaemia; severe hypoglycaemia (symptoms consistent with hypoglycaemia, BG <50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose or glucagons administration and the requirement of third party assistance); nocturnal hypoglycaemia (while patient was asleep) **glycaemic excursions**: yes, blood glucose profiles **total daily dose**: yes **weight change**: BMI **complication rates**: no **adverse events**: yes **health-related quality of life**: no **other**: none **timing of assessment**: baseline, 2, 4, 6, 8, 12, 16, 20 and 24 weeks after randomisation
Wang 2007 [185] China	**focus**: effect of insulin glargine as basal insulin	**total number**: 24 **N glargine**: 16	**glargine**: insulin glargine plus extended-release glipizide (glucotrol XL)	**primary**: unclear **HbA1c**: HbA1c

Study	Design	Participants	Interventions	Outcome measures
	replacement versus NPH insulin in patients with type 2 diabetes, in whom blood glucose was not well controlled with sulphonylureas **design**: randomised controlled trial **single centre** **duration**: 12 weeks **follow-up**: no post-intervention follow-up **setting**: unclear **funding**: not reported	**N NPH**: 8 **inclusion criteria**: type 2 diabetes for six months; age 30 to 70 years; blood glucose not well controlled (FBG ≥7.0 mmol/L and <13.0 mmol/L); treatment with sulphonylurea (equivalent to 7.5 mg/day glibenclamide) or combination treatment with oral agents for >3 months **exclusion criteria**: obvious renal, liver or heart disease **age**: glargine: 57 SD6 years; NPH: 56 SD8 years **gender**: glargine: 43.8% female; NPH: 50% female **BMI: glargine**: 24.2 SD2.8 kg/m2; NPH: 24.6 SD2.5 kg/m2 **ethnicity**: not reported, presumably all Chinese **diabetes duration**: glargine: 10.4 SD4.3 years; **NPH**: 9.5 SD4.9 years **previous medication**: not reported **comorbidities**: not reported **subgroups**: none	**NPH**: NPH insulin plus extended-release glipizide (glucotrol XL) **both**: extended-release glipizide (glucotrol XL) 5 mg/day before breakfast; glargine or NPH injected at bedtime, initial dose 0.15 IU/kg/day; dose titrated every 3 days by the patient with instructions from researchers until FBG was <6.7 mmol/L. **co-interventions**: none **adherence assessment**: no **screening phase**: diabetes education; previous oral antihyperglycaemic therapy stopped and patients treated with extended-release glipizide 5mg/day before breakfast for 2 weeks	**hypoglycaemia**: yes; hypoglycaemic event defind as a sensor glucose value of <3.5 mmol/L for >15 min. **glycaemic excursions**: yes, continuous glucose monitoring system **total daily dose**: yes **weight change**: yes; weight and BMI **complication rates**: no **adverse events**: no **health-related quality of life**: no **other**: none **timing of assessment**: baseline and week 12
previous insulin – detemir versus NPH insulin				
Montanana 2008 (PREDICTIVE-BMI trial) [178] Spain	**focus**: weight change caused by detemir or NPH used as part of basal-bolus regimen in already overweight type 2 diabetes patients **design**: open parallel group randomised controlled trial **multi-centre** **duration**: 26 weeks	**total number**: 271 **N detemir**: 126; 125 completed the trial **N NPH**: 151; 146 completed the trial **inclusion criteria**: men or women ≥18 years, type 2 diabetes, had been receiving 2 daily doses (at least one premix) for ≥3 months; HbA1c between 7.5 and 11%; BMI between 25 and 40 kg/m2 **exclusion criteria**: patients receiving oral glucose-lowering drugs (other than metformin); daily insulin dose ≥2 IU/kg; any condition rendering the patient unsuitable to participate; anticipated changes in concomitant medications known to interfere with	**detemir**: once daily (evening) detemir **NPH**: once daily (evening) NPH **both**: basal insulin continually and individually titrated, aiming for pre-breakfast plasma glucose of ≤6.1 mmol/L without levels of hypoglycaemia considered unacceptable to the patient	**primary**: weight change **HbA1c**: yes **hypoglycaemia**: yes; all, major (third-party assistance required), minor (self-managed, plasma glucose confirmed ≤3.0 mmol/L), nocturnal hypoglycaemic events **glycaemic excursions**: no

Study	Design	Participants	Interventions	Outcome measures
	follow-up: no post-intervention follow-up **setting**: unclear **funding**: Novo Nordisk	glucose metabolism; proliferative retinopathy or maculopathy requiring acute treatment in the preceding 6 months; uncontrolled hypertension; pregnancy and breastfeeding **age**: detemir: 62.1 SD9.3 years; C: 61.8 SD8.3 years **gender**: detemir: 62.4% female; C: 56.8% female **BMI / weight**: detemir: 31.6 SD4.3 kg/m2 / 79.5 SD11.9 kg; C: 32.0 SD4.2 kg/m2 / 82.2 SD12.2 kg **ethnicity**: 99% white **diabetes duration**: detemir: 16.2 SD8.7 years; C: 16.4 SD7.4 years **previous medication**: detemir: 50.4% metformin use; C: 57.5% metformin use **comorbidities**: not reported **subgroups**: none	**co-interventions**: all patients received insulin aspart at main meals (individually titrated aiming for postprandial glucose levels of ≤10.0 mmol/L); concomitant treatment with metformin also allowed adherence assessment: not reported	**total daily dose**: yes **weight change**: yes **complication rates**: no **adverse events**: yes **health-related quality of life**: no **other**: none **timing of assessment**: five clinic visits after randomisation
insulin-naïve – detemir versus NPH insulin				
Philis-Tsimikas 2006 [180] Denmark, France, Italy, The Netherlands, Norway, Spain, USA	**focus**: effectiveness and tolerability of detemir versus NPH once daily with one or more oral anti-diabetic in people with poorly controlled type 2 diabetes **design**: multi-centre, randomised, open-label, 3-arm parallel trial **multi-centre** **duration**: 20 weeks **follow-up**: no post-**intervention follow-up** **setting**: outpatient clinic **funding**: Novo	**total number**: 504 enrolled, 498 in ITT analysis **N morning detemir**: 165, 149 completed the trial **N evening detemir**: 169, 154 completed the trial **N evening NPH**: 164, 149 completed the trial **inclusion criteria**: age ≥18 years, BMI ≤40 kg/m2, diagnosis of type 2 diabetes since at least 12 months, insulin-naïve, HbA1c between 7.5 and 11% after at least 3 months' treatment with one or more oral anti-diabetic agent (OAD); OAD therapy was therapy with metformin or an insulin secretagogue or a combination of the two, at least half the recommended maximum dose; at US centres, concomitant treatment with thiazolidinediones (TZD) was permitted throughout study period, at European centres TZD was to be discontinued before initiation of insulin treatment; use of alpha-glucosidase inhibitor was permitted but only in combination with another OAD **exclusion criteria**: proliferative retinopathy/maculopathy requiring treatment,	**N morning detemir**: insulin detemir once daily before breakfast **N evening detemir**: insulin detemir once daily in the evening (=interval 1 hour before last meal until bedtime) **N evening NPH**: human NPH insulin once daily in the evening **all groups**: insulin injected via pen device, participants advised to keep time of injection constant and to inject insulin subcutaneously, preferably in the thigh, but to rotate sites; initial dose of treatment was 10 IU (U),	**primary**: HbA1c **HbA1c**: yes **hypoglycaemia**: yes; major episodes (requiring third party assistance), confirmed episodes (plasma glucose reading <3.1 mmol/L, patients able to self-manage the event), nocturnal hypoglycaemia (between 11 pm and 6 am) **glycaemic excursions**: 9-point self-measured plasma glucose profiles (using capillary blood and plasma-calibrated monitor): immediately before and 90 min after main meals, bedtime, 3

Study	Design	Participants	Interventions	Outcome measures
	Nordisk	hypoglycaemia unawareness or recurrent major hypoglycaemia, use or anticipated use of ≥1 drug likely to affect blood glucose regulation (e.g. systemic steroids, nonselective beta-blockers, monoamine oxidase inhibitors), OAD treatment not adhering to approved labelling in the respective country; any disease or condition that would make patient unsuitable for participation (e.g. renal, hepatic, cardiac disease), uncontrolled hypertension, any psychological incapacity or language barrier precluding adequate understanding or cooperation **age**: **morning detemir**: 58.3 SD10.4 years; **evening detemir**: 58.7 SD10.2 years; **NPH insulin**: 58.4 SD11.0 years **gender**: **morning detemir**: 40.6% female; **evening detemir**: 46.2% female; **NPH insulin**: 42.7% female **BMI / weight**: **morning detemir**: 29.8 SD5.0 kg/m2; **evening detemir**: 29.7 SD5.1 kg/m2; **NPH insulin**: 30.4 SD4.8 kg/m2 **ethnicity**: not reported **diabetes duration**: **morning detemir**: 10.5 SD7.6 years; **evening detemir**: 10.5 SD7.0 years; NPH **insulin**: 10.0 SD6.9 years **previous medication**: **morning detemir**: 26.1% OAD monotherapy (9.7% metformin, 16.4% secretagogue), 73.9% combination therapy (56.4% metformin + 1 or 2 secretagogues, 5.5% metformin + secretagogue + TZD, 6.7% 2 secretagogues, 1.8% secretagogue + TZD); **evening detemir**: 21.3% OAD monotherapy (8.3% metformin, 13.0% secretagogue), 78.7% combination therapy (53.8% metformin + 1 or 2 secretagogues, 8.9% metformin + secretagogue + TZD, 7.7% 2 secretagogues, 1.2% secretagogue + TZD); NPH insulin: 24.4% OAD monotherapy (9.8% metformin, 14.6% secretagogue), 75.6% combination therapy (53.0 % metformin + 1 or 2 secretagogues, 6.1% metformin + secretagogue + TZD, 9.1% 2 secretagogues, 1.2%	doses were titrated at clinic visits or by telephone at least once every 4 weeks based on the mean of 3 plasma glucose levels measured on 3 consecutive days; in patients receiving detemir in the morning, the dose was titrated to aim for pre-dinner plasma glucose concentration of ≤6.0 mmol/L; in patients receiving detemir or NPH in the evening, titration was aimed to achieve pre-breakfast plasma glucose concentration of ≤6.0 mmol/L **co-interventions**: OAD therapy and dose was to remain unchanged; other co-interventions (similar between groups): ~21% used acetylsalicylic acid, ~19% simvastatin, ~15% atorvastatin **adherence assessment**: not reported	am; additional measurements when patients experienced symptoms indicative of hypoglycaemia **total daily dose**: yes weight change: yes (calibrated scales) **complication rates**: no adverse events: adverse events, standard laboratory analyses, fundoscopy, physical examination **health-related quality of life**: no **other**: none **timing of assessment**: at least 9 telephone contacts and 6 clinic visits (including screening and randomisation)

Study	Design	Participants	Interventions	Outcome measures
		secretagogue + TZD) **comorbidities**: ~56% hypertension, ~29% hypercholesterolaemia, ~12% dyslipidaemia, ~11% diabetic retinopathy; similar occurrence in treatment groups **subgroups**: none		
insulin-naïve – glargine versus detemir				
Rosenstock 2008 [177] Europe, USA	**focus**: comparison of clinical outcomes following supplementation of oral glucose-lowering drugs with with basal insulin analogues detemir and glargine in patients with type 2 diabetes **design**: open-label, parallel group randomised controlled non-inferiority trial **multi-centre** **duration**: 52 weeks **follow-up**: no post-intervention follow-up **setting**: unclear **funding**: Novo Nordisk	**total number**: 582 **N detemir**: 291, 231 completed the trial **N NPH**: 291, 252 completed the trial **inclusion criteria**: insulin-naïve men or women ≥18 years, type 2 diabetes with ≥12 months disease duration; HbA1c between 7.5 and 10%; BMI ≤40 kg/m2; had been receiving one or two oral agents (metformin, insulin secretagogues, alpha-glucosidase inhibitors) ≥4 months on at least half of maximum recommended dose **exclusion criteria**: treatment with thiazolidinediones; use of more than two oral agents within 6 months; hypoglycaemic unawareness; other medical conditions likely to interfere with trial conduct; withdrawal criteria included pregnancy, HbA1c >11% after the first 12 weeks of treatment, initiation of medication interfering with glucose metabolism **age**: detemir: 58.4 SD10.2 years; glargine: 59.4 SD9.6 years **gender**: detemir: 43% female; glargine: 41.2% female **BMI / weight**: detemir: 30.6 SD4.8 kg/m2 / 87.4 SD16.6 kg; glargine: 30.5 SD4.6 kg/m2 / 87.4 SD17.4 kg **ethnicity**: detemir: 86% White, 7.6% Black, 2.4% Asian-Pacific Islanders, 4% other; glargine: 90.4% White, 4.1% Black, 2.4% Asian-Pacific Islanders, 3.1% other **diabetes duration**: detemir: 9.1 SD6.1 years;	**detemir**: once daily (evening) detemir or twice daily (morning and evening) (55% used twice daily injections) **glargine**: once daily (evening) **both**: basal insulin initiated at once daily (evening) 12 U and titrated according to a structured treatment algorithm; people on detemir were allowed to receive an additional morning dose is pre-dinner PG was >7.0 mmol/L, but only if pre-breakfast PG was <7.0 mmol/L or nocturnal hypoglycaemia (major episode or PG ≤4.0 mmol/L) precluded the achievement of the fasting plasma glucose (FPG) target; injection of insulin using pen-injector; FPG target ≤6.0 mmol/L in the absence of hypoglycaemia **co-interventions**: oral glucose-lowering therapy, diet and physical activity	**primary**: HbA1c **HbA1c**: yes; proportion of participants achieving HbA1c ≤7.0% with and without hypoglycaemia **hypoglycaemia**: yes; major (assistance from another person required), minor (confirmed by PG <3.1 mmol/L) symptoms only (PG ≥3.1 mmol/L or no measurement made), nocturnal **glycaemic excursions**: within-participant variation in PG; 10-point self-measured PG profiles **total daily dose**: yes **weight change**: yes **complication rates**: no **adverse events**: yes **health-related quality of life**: no **other**: fasting plasma glucose **timing of assessment**: 16 scheduled visits, during first 12 weeks

Study	Design	Participants	Interventions	Outcome measures
		glargine: 9.1 SD6.4 years **previous medication**: detemir: montherapy 25% (11% metformin, 14% insulin secretagogues); combination therapy 75% (97% metformin + secretagogue); glargine: montherapy 24% (11% metformin, 13% insulin secretagogues); combination therapy 76% (97% metformin + secretagogue) **comorbidities**: not reported **subgroups**: none	recommended to remain stable during the study; no meal-time insulin allowed **adherence assessment**: not reported	weekly investigator contact

10.6 Appendix 6: Charcteristics of included trials - insulin plus pioglitazone versus insulin

Study	Design	Participants	Interventions	Outcome measures
Asnani 2006 USA [238]	**focus**: effect of pioglitazone on vascular reactivity in patients with insulin-treated type 2 diabetes **design**: randomised, double-blind, placebo-controlled trial **single centre** **duration**: 4 months **follow-up**: no post-intervention follow-up **funding**: Takeda, NIH	**total number**: 20 **N PIO + ins**: 10; 8 completed the trial **N P + ins**: 10; 8 completed the trial **inclusion criteria**: age 18-75, insulin-treated type 2 diabetes (with or without oral antidiabetic agents), poor glycaemic control (HbA1c >7.5%) **exclusion criteria**: active liver disease, pregnant or breast-feeding women, history or recent myocardial infarction within last 6 months, recent major surgery within last 6 months **age**: PIO + ins: 59 SD6 years; P + ins: 57 SD5 years **gender**: not reported **BMI**: not reported **ethnicity**: not reported **diabetes duration**: not reported **previous medication**: not reported **comorbidities**: not reported **subgroups**: none	**PIO + ins**: pioglitazone 30 mg at breakfast, insulin continued as before **P + ins**: placebo, insulin continued as before **co-interventions**: stable lipid-lowering (statins) and antihypertensive therapy (including ACE inhibitors in all); not changed during therapy **adherence assessment**: not reported **screening/titration phase**: unclear	**primary**: flow-mediated dilatation **HbA1c**: yes **hypoglycaemia**: no **glycaemic excursions**: no **total daily dose**: no **weight change**: no **complication rates**: no **adverse events**: no health-related quality of life: no **other**: brachial artery reactivity; laboratory assessments, lipid profile **timing of assessment**: baseline, 4 months

Study	Design	Participants	Interventions	Outcome measures
Berhanu 2007 USA [231]	**focus**: safety and efficacy of pioglitazone administered alone or in combination with metformin in reducing insulin dosage requirements for improved glycaemic control in patients with type 2 diabetes **design**: randomised, double-blind, placebo-controlled trial **multi-centre** **duration**: 20 weeks **follow**-up: no post-intervention follow-up **funding**: Takeda Global R&D Centre	**total number**: 220 **N PIO + ins**: 110; 96 completed the trial **N P + ins**: 112; 102 completed the trial **inclusion criteria**: patients with documented type 2 diabetes; age 18-80 years; could self-monitor blood glucose; previous combination therapy failed (HbA1c ≥8.0%) ≤3 months before screening (combination therapy = sulphonylurea plus metformin, insulin plus metformin after failed sulphonylurea, or insulin alone after failed combination therapy with metformin and sulphonylurea (>50% maximum sulphonylurea and ≥2000 mg/day metformin required); C-peptide ≥0.7 ng/ml; FPG >120 mg/dL **exclusion criteria**: thiazolidinediones use <30 days or insulin treatment >30 months before screening; BMI <20 or >45 kg/m2; history of myocardial infarction, acute cardiovascular event, or cerebrovascular accident <6 months before screening; cardiac rhythm disturbance; significant cardiovascular disease including NYHA class III or IV; uncontrolled hypertension; LDL ≥175 mg/dL, triglycerides >500 mg/dL; ALT >1.5 times upper limit of normal; diabetic nephropathy or anaemia **age**: **PIO + ins**: 52.9 SD11.33 years; **P + ins**: 52.5 SD11.07 years **gender**: **PIO + ins**: 56.4% female; **P + ins**: 58.9% female **BMI**: **PIO + ins**: 30.7 SD6.09 kg/m2; **P + ins**: 31.8 SD6.2 kg/m2	**PIO + ins**: pioglitazone titrated to 45 mg/day during first 4 weeks of treatment, plus insulin as below **P + ins**: identical placebo plus insulin as below **both groups**: all patients received one or multiple daily injections of Humalog, Humulin 70/30 or Humulin N; insulin adjusted to achieve FPG <140 mg/dL while avoiding hypoglycaemia **co-interventions**: excluded medications before and during study; hydrochlorothiazide (at doses >25 mg/day), glucocorticoids, steroid injections for joints, niacin; concurrent use of weight-loss agents and antidiabetic medications not included in the study were not permitted; patients maintained stable metformin and, as applicable, previous statin use for duration of study; 98.2% in both groups used metformin; 30.9% in pio group and 28.6% in placebo group used statins **adherence assessment**: pill counts (99.1 to 99.4% adherence) **screening/titration phase**: 1 week screening; instructions on insulin use and up to one week sulphonylurea discontinuation as applicable; insulin initiated and titrated to achieve FPG <140 and >70 mg/dL for 4 additional weeks; after titration period, insulin type, dose and administration schedule were left to the discretion of the clinical investigator; during titration period, instructions regarding	**primary**: change in insulin dosage from baseline to study end **HbA1c**: yes **hypoglycaemia**: hypoglycaemic events (self-monitored blood glucose <60 mg/dL or laboratory value <70 mg/dL, more than two simultaneous hypoglycaemia symptoms relieved by oral glucose-containing substance, or resulting in needing assistance for simple tasks) **glycaemic excursions**: no **total daily dose**: yes **weight change**: weight **complication rates**: no **adverse events**: yes; clinical examinations; ECG; ALT **health-related quality of life**: no **other**: lipid parameters, C-peptide **timing of assessment**: visits every two weeks for the first month, once a month thereafter

Study	Design	Participants	Interventions	Outcome measures
		ethnicity: **PIO + ins**: Hispanic 50.0%, non-Hispanic white 34.9%, non-Hispanic black 12.7%, other 2.7%; **P + ins**: Hispanic 58.9%, non-Hispanic white 25.9%, non-Hispanic black 11.6%, other 3.6% **diabetes duration**: **PIO + ins**: 7.7 SD6.15 years; **P + ins**: 8.5 SD5.43 years **previous medication**: **PIO + ins**: sulphonylureas plus metformin 90.0%, insulin and metformin 8.2%, insulin only 1.8%; **P + ins**: sulphonylureas plus metformin 92.9%, insulin and metformin 5.4%, insulin only 1.8% **comorbidities**: not reported **subgroups**: none	diabetes, hypoglycaemia, nutrition, exercise; patients were randomised if FPG <140 mg/dL achieved during titration	
Fernandez 2008 USA [232]	**focus**: relationship between glycaemic control, vascular reactivity and inflammation in type 2 diabetes **design**: double-blind, placebo-controlled randomised controlled trial **single centre** **duration**: 36 weeks **follow-up**: no post-intervention follow-up **funding**: American Diabetes Association, Takeda Pharmaceuticals	**total number**: 30 **N PIO + ins**: 10 **N P + ins**: 10 **N ramipril + ins**: 10 (not considered here) **inclusion criteria**: adult Mexican-Americans with type 2 diabetes requiring insulin therapy (HbA1c >8.0% despite optimised oral therapy); patients on insulin combination therapy with metformin, sulphonylureas or meglitinides included **exclusion criteria**: insulin combination therapy with thiazolidinediones **age**: mean age ~46 years (no details) **gender**: overall ~60% female (no details) **BMI**: overall ~31-33 kg/m2 (no details) **ethnicity**: Mexican-American	**PIO + ins**: pioglitazone 45 mg/day; started at 15 mg daily and then increased to 30 mg daily in week 2 and to 45 mg daily in week 4 **P + ins**: placebo **ramipril + ins**: ramipril 10 mg/day (not considered here) **all groups**: 3-day comprehensive diabetes education and nutritional programme; patients could select between insulin therapy using multiple daily injections (basal-bolus therapy using combination of insulin glargine at bedtime plus premeal insulin aspart) or continuous subcutaneous infusion (Meditronic/Minimed or Animas pump using basal infusion and premeal boluses of insulin aspart); insulin dose adjusted to achieve the	**primary**: vascular analyses **HbA1c**: yes **hypoglycaemia**: yes (symptomatic hypoglycaemia requiring glucose ingestion) **glycaemic excursions**: no **total daily dose**: yes **weight change**: yes **complication rates**: no **adverse events**: yes **health-related quality of life**: no **other**: euglycaemic-hyperinsulinaemic clamp; vascular studies; lipid parameters **timing of assessment**: clinic visits at 2- to 4-week

Study	Design	Participants	Interventions	Outcome measures
		diabetes duration: 6.2-8.4 years **previous medication**: use of oral antidiabetic medications similar between groups **comorbidities**: not reported **subgroups**: none	following glycaemic goals: fasting and pre-meal capillary blood glucose 80 – 120 mg/dL, 2-h post-meal glucose <160 mg/dL, bedtime glucose <140 mg/dL **co-interventions**: patients on ACE-inhibitors or angiotensin II receptor blockade were switched to alpha-methyl dopa (at least 2 months before study) and the dose adjusted to re-establish blood pressure control (<130/80 mmHg) before enrolment; other medication allowed if stable for at least 3 months; nearly half the patients were using a statin and one third was on antihypertensive therapy **adherence assessment**: compliance with treatment ascertained during each visit (no details) **screening phase**: no	intervals during first 3 months, every 2 months thereafter
Mattoo 2005 Worldwide [233]	**focus**: effect of pioglitazone plus insulin versus placebo plus insulin on glycaemic control, serum lipid profile, and selected cardiovascular risk factors in patients with type 2 diabetes whose disease was inadequately controlled with insulin therapy alone, despite efforts to intensify the treatment **design**: randomised double-blind, placebo-controlled parallel group trial	**total number**: 289 **N PIO + ins**: 142; 128 completed the trial **N P + ins**: 147; 135 completed the trial **inclusion criteria**: type 2 diabetes diagnosed according to WHO criteria, use of insulin therapy (with or without oral antihyperglycaemic medication) for ≥3 months, HbA1c ≥7.5% at screening, ≥30 years at diagnosis **exclusion criteria**: type 1 diabetes, clinical signs or symptoms of any chronic systemic condition (defined), signs or symptoms of drug or alcohol abuse; previous therapy with thiazolidinediones, systemic glucocorticoid therapy, nicotinic acid at	**PIO + ins**: 30 mg pioglitazone plus insulin **P + ins**: identical placebo plus insulin **both**: all patients received diabetes education, including dietary and exercise guidelines, and were instructed to maintain their individual diet and exercise regimens throughout the study; patient diaries for self-monitoring blood glucose; insulin dose reduced by 10% at randomisation to avoid hypoglycaemia and adjusted thereafter based on self-monitored blood glucose (SMGB) levels **co-interventions**: patients were allowed to use other medication as	**primary**: change in HbA1c level from baseline to endpoint **HbA1c**: HbA1c **hypoglycaemia**: yes (1. subjective symptoms only, 2. subjective symptoms with SMBG ≥2.8 mmol/L, 3. subjective symptoms with SMBG <2.8 mmol/L, 4. SMBG <2.8 mmol/l without symptoms) **glycaemic excursions**: no **total daily dose**: yes **weight change**: yes **complication rates**: no **adverse eve**nts: yes;

Study	Design	Participants	Interventions	Outcome measures
	multi-centre **duration**: 6 months **follow-up**: no post-intervention follow-up **funding**: Eli Lilly, Takeda Europe	>500 mg/d, or therapy for malignancy other than basal cell or squamous skin cancer; women breastfeeding or pregnant, women of childbearing potential without active birth control **age**: **PIO + ins**: 58.8 SD7.4 years; **P + ins**: 58.9 SD6.9 years **gender: PIO + ins**: 56.3% female; **P + ins**: 57.1% female **BMI: PIO + ins**: 32.5 SD4.8 kg/m2; **P + ins**: 31.8 SD5.0 kg/m2 **ethnicity**: not reported **diabetes duration**: **PIO + ins**: 163.4 SD81.0 months; **P + ins**: 160.9 SD73.7 months **previous medication**: 149 patients previously on oral agents (metformin n=109, sulphonylurea n=19, metformin plus sulphonylurea n=17, other n=4 **comorbidities**: not reported **subgroups**: none	required, except another oral antidiabetic agent, systemic glucocorticoid therapy, or nicotinic acid (>500 mg/d) **adherence assessment**: capsule count (compliance rate ≥97.2%) **screening phase**: up to 14 days lead-in phase, patients remained on prescribed insulin therapy regimen, as monotherapy or with oral antihyperglycaemic agent; patients with HbA1c ≥7.5% then proceeded to insulin intensification period (3 months): insulin dose and number of injections adjusted to achieve fasting and preprandial blood glucose <5.5. mmol/L and 2-h postprandial blood glucose <7.5 mmol/L; patients with HbA1c ≥7.0% after insulin intensification were randomised to pioglitazone plus insulin or placebo plus insulin	adverse events, laboratory testing, physical examination **health-related quality of life**: no **other**: lipid parameters **timing of assessment**: 5 visits between randomisation and end of study
Raz 2005 Worldwide [234]	**focus**: efficacy and safety of biphasic insulin aspart 30/70 (BIAsp 30) plus pioglitazone versus glibenclamide plus pioglitazone and BIAsp 30 monotherapy in type 2 diabetes **design**: randomised, open-label, parallel group trial **multi-centre** **duration**: 18 weeks	**total number**: 283 **N PIO + ins**: 93; 73 completed the trial **N PIO + glibenclamide**: 93; 56 completed the trial (not considered here) N ins mono: 97; 75 completed the trial **inclusion criteria**: male and female patients with type 2 diabetes; age ≥18 years; BMI ≤40 kg/m2; treatment with sulphonylurea (SU) (monotherapy or combination therapy) ≥3 months before screening; insufficient glycaemic control (HbA1c 7.4 – 14.7%) **exclusion criteria**: significant disease	**PIO + ins**: 30 mg pioglitazone once daily after breakfast plus biphasic insulin aspart 30/70 (BIAsp 30). BIAsp 30 initiated at a dose of 0.2 U/kg/day. **PIO + glibenclamide**: 30 mg pioglitazone once daily after breakfast plus glibenclamide (starting dose 5 mg in patients already on glibenclamide, equivalent dose not exceeding 10 mg in patients previously on other sulphonylureas) (not considered here) **ins mono**: BIAsp 30 initiated at a	**primary**: end of trial HbA1c **HbA1c**: yes **hypoglycaemia**: major hypoglycaemic episodes (patient unable to self-treat, blood glucose <50 mg/dL, or when symptoms remitted after administration of intravenous glucose or intramuscular glucagons after food intake); minor hypoglycaemic episodes (blood glucose <50 mg/dL, patient handled the event without assistance from

Study	Design	Participants	Interventions	Outcome measures
	follow-up: no post-intervention follow-up **funding**: Novo Nordisk	or conditions likely to affect trial or health outcomes (including history of drug or alcohol dependence, impaired hepatic function, cardiac disease) **age: PIO + ins**: 56.7 SD10.5 years; **ins mono**: 55.2 SD9.1 years **gender: PIO + ins**: 47% female; **ins mono**: 35% female **BMI: PIO + ins**: 29.4 SD4.6 kg/m2; in**s mono**: 29.5 SD4.9 kg/m2 **ethnicity**: not reported **diabetes duration: PIO + ins**: 9.2 SD5.3 years; **ins mono**: 10.0 SD5.8 years **previous medication**: patients taking other oral agents with SU: **PIO + ins**: none 14.0%, acarbose 9.7%, meglitinides 3.2%, metformin 83.9%, thiazolidinediones 7.5%; **ins mono**: none 13.4%, acarbose 12.4%, meglitinides 1.0%, metformin 80.4%, thiazolidinediones 4.1% **comorbidities**: not reported **subgroups**: none	dose of 0.3 U/kg/day **insulin therapy**: biphasic insulin aspart 30/70 (30% rapid-acting soluble insulin aspart, 70% intermediate-acting protamine-crystallised insulin aspart); BIAsp 30 injected immediately (within 5 mins) before breakfast (50% of dose) and before dinner (50% of dose); BIAsp 30 titrated individually by patients using self-monitored blood glucose (SMBG) to achieve target blood glucose values of 5 to 8 mmol/L for fasting, preprandial and nighttime measurements, and 5 to 10 mmol/L for postprandial readings; BIAsp 30 injections with NovoPen 3; all dose titrations completed within 8 weeks of treatment **co-interventions**: any patient treated with insulin sensitiser other than pioglitazone was told to stop treatment 14 days before randomisation; no manipulation of lipid lowering regimens **adherence assessment**: checking patient diaries **screening phase**: none	others); symptomatic episodes (hypoglycaemic symptoms present but not confirmed by blood glucose measurement, assistance from others not required) **glycaemic excursions**: yes, blood glucose profiles (7 and 8 point) **total daily dose**: yes **weight change**: weight **complication rates**: no **adverse events**: yes **health-related quality of life**: no **other**: lipid profiles **timing of assessment**: screening, 8 weeks, end of trial (HbA1c); baseline, 4, 8, 12, 18 weeks (lipids)
Rosenstock 2002 (pioglitazone 014 study group) USA [235]	**focus**: effect of two doses of pioglitazone (15 or 30 mg) in combination with a stable insulin regimen to improve glycaemic control in patients whose type 2 diabetes is poorly controlled despite current insulin	**total number**: 566 **N PIO15 + ins**: 191; 161 completed the trial **N PIO30 + ins**: 188; 172 completed the trial **N P + ins**: 187; 164 completed the trial **inclusion criteria**: 30 to 75 years, type 2 diabetes; insulin treatment for ≥30 units/day for ≥months, with stable	**N PIO15 + ins**: 15 mg pioglitazone plus usual insulin regimen **N PIO30 + ins**: 30 mg pioglitazone plus usual insulin regimen **N P + ins**: placebo plus usual insulin regimen **all**: insulin dose could be decreased in response to hypoglycaemia; maximum permitted decrease in	**primary**: unclear, presumably HbA1c at study endpoint **HbA1c**: yes **hypoglycaemia**: yes; defined as FPG ≤100 mg/dL (5.6 mmol/L), symptoms of hypoglycaemia not explained by other

Study	Design	Participants	Interventions	Outcome measures
	therapy **design**: double-blind, placebo-controlled randomised controlled trial **multi-centre** **duration**: 16 weeks **follow-up**: no post-intervention follow-up **funding**: Takeda Pharmaceuticals	dosage for at least 30 days; at screening HbA1c ≥8.0%, fasting C-peptide >0.7 µg/L **exclusion criteria**: history of ketoacidosis, unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; impaired hepatic function (AST, ALT, total bilirubin or alkaline phosphatase >2.5 times upper limit of normal; impaired kidney function (serum creatinine >1.8 mg/dL); anaemia; unstable or symptomatic cardiovascular or cerebrovascular conditions (defined) **age: PIO15 + ins**: 56.9 SE10.4 years; **PIO30 + ins**: 57.5 SE9.9 years; **P + ins**: 56.7 SE9.4 years **gender: PIO15 + ins**: 53.9% female; **PIO30 + ins**: 49.5% female; **P + ins**: 54.5% female **BMI: PIO15 + ins**: 33.2 SE5.4 kg/m2; **PIO30 + ins**: 34.3 SE6.2 kg/m2; **P + ins**: 33.2 SE5.2 kg/m2 **ethnicity: PIO15 + ins**: 74.9% Caucasian; **PIO30 + ins**: 73.4% Caucasian; **P + ins**: 71.1% Caucasian **diabetes duration**: not reported previous medication: 88% insulin monotherapy; 12% combination with oral agents (8% metformin, 2% glyburide, 2% glipizide); 134 patients receiving serum lipid reducing agent (classes approximately evenly distributed across groups) **comorbidities**: not reported **subgroups**: none	insulin dose at any one time: 10% of patient's current total daily dosage; reduced dose remained fixed unless new occurrences of hypoglycaemia warranted another 10% decrease co-interventions: lipid-lowering medications allowed, provided patient had been taking stable dose for >60 days and regimen was continued without alteration throughout the study; no dietary intervention / modification **adherence assessment**: no **screening phase**: 2 weeks; patients on oral antihyperglycaemic agent in addition to insulin discontinued oral agent at beginning of screening period; screening followed by one week (for patients on stable insulin monotherapy) or four weeks (for patients previously on insulin plus oral agents) single-blind placebo treatment period (stable insulin regimen in combination with placebo)	conditions **glycaemic excursions**: no **total daily dose**: yes **weight change**: yes **complication rates**: no **adverse events**: yes; laboratory values, vital signs, ECGs, any adverse events **health-related quality of life**: no **other**: serum lipid measurements (triglycerides and cholesterol) **timing of assess**ment: patients seen every four weeks
Scheen 2006	**focus**: effects of	**total number**: 1760	**PIO + ins**: pioglitazone plus previous	**primary**: (of PROactive

Study	Design	Participants	Interventions	Outcome measures
19 European countries [236] part of PROactive trial (investigating only patients concomitantly treated with insulin) abstract only	pioglitazone on the secondary prevention of macrovascular events in type 2 diabees **design**: randomised double-blind outcome study **multi-centre** **duration**: mean 34.5 months **follow-up**: no post-intervention follow-up **funding**: Takeda Europe, Eli Lilly	**N PIO + ins**: 864 **N P + ins**: 896 **inclusion criteria**: male or female with type 2 diabetes; age 35 to 75 years; HbA1c level above the upper limit of normal (local equivalent of 6.5% for a Diabetes Control and Complications Trial-traceabel assay), despite management of diabetes with diet alone or with oral blood glucose lowering agents; increased risk of macrovascular disease as defined in the trial; insulin allowed if given in combination with oral agents **exclusion criteria**: current use of pioglitazone or any other thiazolidinediones; signs of type 1 diabetes; insulin as sole therapy for diabetes; planned revascularisation; symptomatic heart failure; leg ulcers, gangrene, or pain at rest; haemodialysis; significantly impaired hepatic function (serum alanine aminotransferase >2.5 times upper limit of normal) **age**: not reported for subgroup on insulin therapy **gender**: not reported for subgroup on insulin therapy **BMI**: not reported for subgroup on insulin therapy **ethnicity**: not reported for subgroup on insulin therapy **diabetes duration**: not reported for subgroup on insulin therapy **previous medication**: at baseline, insulin combined with metformin	treatment; forced titration phase in the first two months of treatment with stepwise increase of pioglitazone dose from 15 mg to 30 mg and then up to 45 mg, to maintain patients at maximum tolerated dose; dose could be adjusted at any time within 15 mg to 45 mg range based on tolerability **P + ins**: placebo plus previous treatment **both**: investigators encouraged to maintain glycaemia at <6.5% **co-interventions**: proportion of concomitant oral therapy remained similar: PIO + ins: metformin alone 47%, sulphonylurea alone 16%, metformin plus sulphonylurea 10%; P + ins: metformin alone 52%, sulphonylurea alone 16%, metformin plus sulphonylurea 11% **adherence assessment**: no **screening phase**: not reported	trial) time from randomisation to any of (composite endpoint): all-cause mortality, non-fatal myocardial infarction, acute coronary syndrome, cardiac intervention (including coronary artery bypass graft or percutaneous coronary intervention), stroke, major leg amputation (above ankle), bypass surgery; or revascularisation in the leg **HbA1c**: yes **hypoglycaemia**: yes (but undefined) **glycaemic excursions**: no **total daily dose**: yes **weight change**: no **complication rates**: not reported here **adverse events**: yes **health-related quality of life**: no **other**: none (in this abstract) **timing of assessment**: unclear

Study	Design	Participants	Interventions	Outcome measures
		monotherapy in 53%, sulphonylurea monotherapy in 24%, dual therapy with metformin and sulphonylurea 12% **comorbidities**: not reported **subgroups**: abstract reports subgroup of larger trial – in the main trial only about one third of patients received concomitant insulin therapy		
Shah 2007 USA [237] abstract only	**focus**: effects of a pioglitazone and insulin combination versus insulin therapy alone on body fat distribution **design**: randomised double-blind placebo-controlled trial **single centre** **duration**: 12 to 16 weeks **follow-up**: no post-intervention follow-up **setting**: unclear **funding**: not stated	**total number**: 25 **N PIO + ins**: 12 **N P + ins**: 13 inclusion criteria: insulin-treated, obese type 2 diabetes patients **exclusion criteria**: not reported **age**: not reported **gender**: not reported **BMI**: 36.5 kg/m2 **ethnicity**: not reported **diabetes duration**: not reported **previous medication**: not reported **comorbidities**: not reported **subgroups**: none	**PIO + ins**: pioglitazone (30 mg titrated to 45 mg) and insulin **P + ins**: placebo and insulin co-interventions: not reported **adherence assessment**: not reported	**primary**: body fat distribution **HbA1c**: HbA1c **hypoglycaemia**: no **glycaemic excursions**: no **total daily dose**: no **weight change**: yes **complication rates**: no **adverse events**: no **health-related quality of life**: no **other**: subcutaneous adipose tissue, visceral adipose tissue (abdominal CT scans) **timing of assessment**: not reported

10.7 Appendix 7: Characteristics of included trials – pioglitazone plus insulin versus pioglitazone

Study	Design	Participants	Interventions	Outcome measures
Raskin 2006 USA [241,242]	**focus**: safety and efficacy of BIAsp 30 (30% soluble and 70%	**total number**: 181 **N BIAsp 30 + met + pio**: 93 **N met + pio**: 88	**BIAsp 30 + met + pio**: BIAsp 30 (30% soluble and 70% protaminated insulin aspart) added to an optimised	**primary**: HbA1c (presumably) **HbA1c**: yes

Study	Design	Participants	Interventions	Outcome measures
abstract only	protaminated insulin aspart) in insulin-naïve type 2 diabetes patients taking any two oral antidiabetic agents **design**: randomised, parallel group trial **single/multi-centre unclear duration**: 34 weeks **follow-up**: no post-intervention follow-up **funding**: Novo Nordisk	**inclusion criteria**: insulin-naïve, type 2 diabetes; HbA1c 7.5-12%, taking any two oral antidiabetic agents **exclusion criteria**: not reported **age**: not reported **gender**: not reported **BMI**: not reported **ethnicity**: not reported **diabetes duration**: not reported **previous medication**: not reported **comorbidities**: not reported **subgroups**: none	treatment of metformin and pioglitazone; BIAsp 30 initiated at 6 U twice a day (prebreakfast and presupper) and titrated to target blood glucose (4.4-6.1 mmol/L) by an algorithm-directed forced titration **met + pio**: optimised treatment of metformin and pioglitazone without insulin **co-interventions**: not reported **adherence assessment**: not reported **run-in phase**: 8-week run-in: treatment changed to metformin (2500 mg/day) and pioglitazone (30 or 45 mg/day)	**hypoglycaemia**: minor hypoglycaemia (blood glucose <3.1 mmol/L) **glycaemic excursions**: no **total daily dose**: no **weight change**: weight **complication rates**: no **adverse events**: yes **health-related quality of life**: no **other**: none **timing of assessment**: not reported

10.8 Appendix 8: Pairwise comparisons

Male BMI 30

Comparison 1 : EXE_GLA vs GLA	No comp			With Comp		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8.607	8.538	0.069	8.394	8.331	0.063
Total QALYs	8.567	8.464	0.103	8.354	8.258	0.096
Direct Drug Cost	£8,813	£7,939	£875	£8,592	£7,727	£865
Total Cost	£18,953	£18,258	£696	£19,469	£18,778	£691
ICER			£6,755			£7,180

Comparison 2 : SIT vs ROSI	No comp			With Comp		
	Sitagliptin	Rosiglitazone	Net	Sitagliptin	Rosiglitazone	Net
UKPDS QALYs	8.566	8.549	0.017	8.347	8.342	0.005
Total QALYs	8.479	8.447	0.032	8.263	8.242	0.021
Direct Drug Cost	£5,793	£5,938	-£145	£5,628	£5,779	-£151
Total Cost	£16,083	£16,277	-£194	£16,650	£16,853	-£203
ICER			-£6,055			-£9,849

Comparison 3 : VIL vs PIO	No comp			With Comp		
	Vildagliptin	Pioglitazone	Net	Vildagliptin	Pioglitazone	Net
UKPDS QALYs	8.561	8.590	-0.029	8.353	8.378	-0.025
Total QALYs	8.468	8.479	-0.011	8.262	8.269	-0.007
Direct Drug Cost	£5,371	£5,824	-£453	£5,220	£5,665	-£445
Total Cost	£15,731	£16,180	-£449	£16,309	£16,756	-£446
ICER			£39,846			£66,799

Comparison 4 : GLA vs NPH	No comp			With Comp		
	Glargine	NPH	Net	Glargine	NPH	Net
UKPDS QALYs	8.538	8.540	-0.002	8.331	8.333	-0.003
Total QALYs	8.464	8.457	0.007	8.258	8.253	0.006
Direct Drug Cost	£7,939	£6,111	£1,828	£7,727	£5,946	£1,780
Total Cost	£18,258	£16,402	£1,855	£18,778	£16,980	£1,798
ICER			£281,349			£320,029

Comparison 5 : DET vs NPH	No comp			With Comp		
	Detemiir	NPH	Net	Detemir	NPH	Net
UKPDS QALYs	8.530	8.540	-0.010	8.316	8.333	-0.018
Total QALYs	8.472	8.457	0.015	8.259	8.253	0.006
Direct Drug Cost	£8,826	£6,111	£2,715	£8,585	£5,946	£2,638
Total Cost	£19,128	£16,402	£2,726	£19,621	£16,980	£2,641
ICER			£187,726			£417,625

Male BMI 30 but no weight changes within UKPDS Outcomes Model

Comparison 1 : EXE_GLA vs GLA	No comp			With Comp		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8.599	8.547	0.053	8.386	8.338	0.048
Total QALYs	8.559	8.472	0.087	8.347	8.265	0.082
Direct Drug Cost	£8,808	£7,945	£863	£8,587	£7,732	£856
Total Cost	£18,999	£18,222	£777	£19,513	£18,740	£773
ICER			£8,967			£9,449

Comparison 2 : SIT vs ROSI	No comp			With Comp		
	Sitagliptin	Rosiglitazone	Net	Sitagliptin	Rosiglitazone	Net
UKPDS QALYs	8.562	8.562	0.000	8.354	8.353	0.001
Total QALYs	8.476	8.460	0.015	8.269	8.253	0.016
Direct Drug Cost	£5,790	£5,947	-£157	£5,632	£5,787	-£154
Total Cost	£16,089	£16,272	-£183	£16,670	£16,848	-£178
ICER			-£11,878			-£11,011

Comparison 3 : VIL vs PIO	No comp			With Comp		
	Vildagliptin	Pioglitazone	Net	Vildagliptin	Pioglitazone	Net
UKPDS QALYs	8.562	8.603	-0.041	8.354	8.389	-0.035
Total QALYs	8.469	8.492	-0.023	8.263	8.279	-0.017
Direct Drug Cost	£5,371	£5,833	-£461	£5,221	£5,672	-£451
Total Cost	£15,745	£16,191	-£446	£16,325	£16,763	-£438
ICER			£19,477			£26,270

Comparison 4 : GLA vs NPH	No comp			With Comp		
	Glargine	NPH	Net	Glargine	NPH	Net
UKPDS QALYs	8.547	8.550	-0.004	8.338	8.341	-0.003
Total QALYs	8.472	8.468	0.005	8.265	8.261	0.005
Direct Drug Cost	£7,945	£6,118	£1,826	£7,732	£5,952	£1,780
Total Cost	£18,222	£16,389	£1,833	£18,740	£16,958	£1,782
ICER			£387,629			£379,631

Comparison 5 : DET vs NPH	No comp			With Comp		
	Detemiir	NPH	Net	Detemir	NPH	Net
UKPDS QALYs	8.535	8.550	-0.015	8.329	8.341	-0.012
Total QALYs	8.477	8.468	0.009	8.272	8.261	0.012
Direct Drug Cost	£8,831	£6,118	£2,713	£8,598	£5,952	£2,646
Total Cost	£19,132	£16,389	£2,743	£19,638	£16,958	£2,680
ICER			£303,770			£226,163

Female BMI 30

Comparison 1 : EXE_GLA vs GLA	No comp			With Comp		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	9.468	9.397	0.071	9.210	9.148	0.062
Total QALYs	9.423	9.318	0.105	9.167	9.071	0.096
Direct Drug Cost	£9,394	£8,385	£1,010	£9,140	£8,143	£997
Total Cost	£19,436	£18,598	£838	£19,969	£19,138	£831
ICER			£7,970			£8,653

Comparison 2 : SIT vs ROSI	No comp			With Comp		
	Sitagliptin	Rosiglitazone	Net	Sitagliptin	Rosiglitazone	Net
UKPDS QALYs	9.436	9.402	0.034	9.175	9.153	0.022
Total QALYs	9.344	9.294	0.050	9.085	9.047	0.038
Direct Drug Cost	£6,244	£6,379	-£135	£6,053	£6,195	-£142
Total Cost	£16,415	£16,568	-£153	£17,003	£17,178	-£175
ICER			-£3,079			-£4,604

Comparison 3 : VIL vs PIO	No comp			With Comp		
	Vildagliptin	Pioglitazone	Net	Vildagliptin	Pioglitazone	Net
UKPDS QALYs	9.428	9.427	0.000	9.175	9.176	-0.001
Total QALYs	9.328	9.310	0.019	9.078	9.061	0.017
Direct Drug Cost	£5,824	£6,265	-£441	£5,646	£6,082	-£437
Total Cost	£15,959	£16,502	-£543	£16,581	£17,112	-£531
ICER			-£29,027			-£30,976

Comparison 4 : GLA vs NPH	No comp			With Comp		
	Glargine	NPH	Net	Glargine	NPH	Net
UKPDS QALYs	9.397	9.395	0.002	9.148	9.147	0.002
Total QALYs	9.318	9.308	0.010	9.071	9.061	0.010
Direct Drug Cost	£8,385	£6,497	£1,887	£8,143	£6,308	£1,835
Total Cost	£18,598	£16,742	£1,856	£19,138	£17,341	£1,797
ICER			£177,940			£179,074

Comparison 5 : DET vs NPH	No comp			With Comp		
	Detemiir	NPH	Net	Detemir	NPH	Net
UKPDS QALYs	9.398	9.395	0.002	9.146	9.147	-0.001
Total QALYs	9.335	9.308	0.027	9.085	9.061	0.024
Direct Drug Cost	£9,310	£6,497	£2,812	£9,039	£6,308	£2,732
Total Cost	£19,538	£16,742	£2,796	£20,048	£17,341	£2,706
ICER			£102,007			£113,988

Male BMI 35

Comparison 1 : EXE_GLA vs GLA	No comp			With Comp		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8.533	8.448	0.085	8.328	8.252	0.076
Total QALYs	8.493	8.375	0.118	8.289	8.180	0.109
Direct Drug Cost	£9,958	£9,863	£96	£9,703	£9,612	£91
Total Cost	£20,311	£20,360	-£49	£20,787	£20,844	-£57
ICER			-£413			-£522

Comparison 2 : SIT vs ROSI	No comp			With Comp		
	Sitagliptin	Rosiglitazone	Net	Sitagliptin	Rosiglitazone	Net
UKPDS QALYs	8.485	8.473	0.012	8.285	8.274	0.011
Total QALYs	8.399	8.371	0.028	8.201	8.174	0.027
Direct Drug Cost	£6,619	£6,767	-£148	£6,438	£6,586	-£147
Total Cost	£17,165	£17,363	-£198	£17,712	£17,906	-£194
ICER			-£7,090			-£7,254

Comparison 3 : VIL vs PIO	No comp			With Comp		
	Vildagliptin	Pioglitazone	Net	Vildagliptin	Pioglitazone	Net
UKPDS QALYs	8.490	8.504	-0.014	8.288	8.302	-0.014
Total QALYs	8.397	8.393	0.004	8.198	8.194	0.004
Direct Drug Cost	£6,111	£6,552	-£441	£5,937	£6,374	-£436
Total Cost	£16,717	£17,095	-£378	£17,264	£17,656	-£392
ICER			-£100,734			-£98,356

Comparison 4 : GLA vs NPH	No comp			With Comp		
	Glargine	NPH	Net	Glargine	NPH	Net
UKPDS QALYs	8.448	8.443	0.005	8.252	8.250	0.002
Total QALYs	8.375	8.361	0.013	8.180	8.169	0.010
Direct Drug Cost	£9,863	£7,349	£2,514	£9,612	£7,162	£2,450
Total Cost	£20,360	£17,857	£2,503	£20,844	£18,415	£2,429
ICER			£189,400			£233,187

Comparison 5 : DET vs NPH	No comp			With Comp		
	Detemiir	NPH	Net	Detemir	NPH	Net
UKPDS QALYs	8.445	8.443	0.001	8.249	8.250	-0.001
Total QALYs	8.387	8.361	0.025	8.192	8.169	0.023
Direct Drug Cost	£11,084	£7,349	£3,734	£10,803	£7,162	£3,641
Total Cost	£21,579	£17,857	£3,722	£22,043	£18,415	£3,627
ICER			£146,632			£157,478

Female BMI 35

Comparison 1 : EXE_GLA vs GLA	No comp			With Comp		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	9.391	9.306	0.085	9.143	9.069	0.074
Total QALYs	9.346	9.227	0.119	9.099	8.991	0.108
Direct Drug Cost	£10,645	£10,388	£257	£10,350	£10,100	£249
Total Cost	£20,907	£20,781	£126	£21,396	£21,289	£107
ICER			£1,058			£988

Comparison 2 : SIT vs ROSI	No comp			With Comp		
	Sitagliptin	Rosiglitazone	Net	Sitagliptin	Rosiglitazone	Net
UKPDS QALYs	9.350	9.329	0.021	9.105	9.087	0.018
Total QALYs	9.258	9.222	0.037	9.015	8.981	0.034
Direct Drug Cost	£7,138	£7,282	-£144	£6,925	£7,069	-£144
Total Cost	£17,542	£17,769	-£227	£18,121	£18,335	-£214
ICER			-£6,205			-£6,315

Comparison 3 : VIL vs PIO	No comp			With Comp		
	Vildagliptin	Pioglitazone	Net	Vildaglipti n	Pioglitazone	Net
UKPDS QALYs	9.347	9.343	0.003	9.103	9.100	0.004
Total QALYs	9.248	9.226	0.021	9.007	8.985	0.022
Direct Drug Cost	£6,627	£7,065	-£439	£6,424	£6,856	-£433
Total Cost	£16,988	£17,458	-£470	£17,598	£18,047	-£449
ICER			-£21,965			-£20,618

Comparison 4 : GLA vs NPH	No comp			With Comp		
	Glargine	NPH	Net	Glargine	NPH	Net
UKPDS QALYs	9.306	9.303	0.003	9.069	9.065	0.003
Total QALYs	9.227	9.216	0.012	8.991	8.980	0.012
Direct Drug Cost	£10,388	£7,796	£2,592	£10,100	£7,576	£2,524
Total Cost	£20,781	£18,208	£2,572	£21,289	£18,792	£2,497
ICER			£219,805			£212,009

Comparison 5 : DET vs NPH	No comp			With Comp		
	Detemiir	NPH	Net	Detemir	NPH	Net
UKPDS QALYs	9.313	9.303	0.010	9.071	9.065	0.006
Total QALYs	9.250	9.216	0.034	9.010	8.980	0.030
Direct Drug Cost	£11,663	£7,796	£3,867	£11,336	£7,576	£3,760
Total Cost	£22,135	£18,208	£3,926	£22,592	£18,792	£3,800
ICER			£114,229			£125,938

Part 2. 6.3 Appendix I3 – Evidence tables for included studies

1 Included studies for the GLP-1 analogue evidence review

1.1 Description of studies

Study	Methods	Participants	Interventions	Outcomes
Barnett 2007 (NOTE: not used to draft evidence statement as not considered a relevant compariso n for this guideline)	TRIAL DESIGN: Open label crossover DURATION OF INTERVENTION: 16 weeks DURATION OF FOLLOW-UP: 16 weeks RUN IN PERIOD: not reported RANDOMISATIO N PROCEDURE: Computer generated central randomization table BLINDING: Open label OVERALL RISK OF BIAS: ++ SOURCE OF FUNDING: Eli Lilly	WHO PARTICIPATED: Patients with type 2 diabetes INCLUSION CRITERIA: Type 2 diabetes, equal to or more than 30 years of age, receiving treatment with either a stable dose of immediate- or extended-release MET equal to or greater than 1500mg/d or an optimally effective dose of SFU for 3 months, HbA1C equal to or more than 7.1% and equal to or less than 11%, BMI more than 25 kg/m2 and less than 40 kg/m2, stable body weight (not varying by more than 10% for at least 3 months prior to screening) EXISTING THERAPY: failing on metformin or sulfonylureas EXCLUSION CRITERIA: not reported NUMBERS: 141 AGE: mean 54 (SD9) DURATION OF DIABETES: EXEN first 6.5 years (4.9) INSULIN first 8.2 years (6.0) HbA1c: 8.9% *SD 1.1) GENDER: EXEN first 52.7% males INSULIN first 45.8% males ETHNIC GROUP: not reported COMORBIDITIES: Not stated COMEDICATIONS: Patients continued prestudy dose of metformin or	NUMBER OF STUDY CENTRES: 26 sites SETTING: Unclear INTERVENTION : Exenatide (EXEN), subcutaneous injection, 10ug/day for 4 weeks then 20ug/day for 12 weeks, administered twice daily CONTROL: Insulin glargine (INSULIN), titrated to fasting blood glucose equal to or <5.6 mmol/l, initiated at 10IU and increased weekly, four times daily) TREATMENT BEFORE STUDY: - Patients had been receiving treatment with either a stable dose of immediate- or extended-release MET equal to or greater than 1500mg/d or an optimally effective dose of SFU for 3 months - Patients	PRIMARY OUTCOMES: HbA1c (change from baseline to end of treatment) SECONDARY OUTCOMES: target HbA1c; bodyweight, fasting serum glucose, fasting serum lipids, 7-point self-monitored blood glucose (SMBG); postprandial (PPG) excursions; safety assessment; adverse events including hypoglycaemia

Study	Methods	Participants	Interventions	Outcomes
		sulfonylurea PHARMACO-NAIIVE:	continued on prestudy dose of MET or SFU	
Davis 2007	TRIAL DESIGN: Parallel open label trial DURATION OF INTERVENTION: 16 weeks DURATION OF FOLLOW-UP:16 weeks RUN-IN PERIOD: not reported RANDOMISATION PROCEDURE: Not reported in detail. 2:1 EXENATIDE: INSULIN BLINDING: None SETTING: 5 centres COUNTRY: USA ITT ANALYSIS: No. Results are only for patients with sufficient data for primary efficacy analysis (n=45 compared with n=49 ITT) DESCRIPTION OF WITHDRAWALS NAD LOSSES TO FOLLOW-UP: Inadequate; number vary in tables SAMPLE SIZE CALCULATION: Yes,; however powered to "verify probability of observing >60% success in Exenatide group" (?) OVERALL RISK OF BIAS: + SOURCE OF FUNDING: : Not specified but some authors declared as employees of Amylin Pharmaceuticals and/or Eli Lilly	WHO PARTICIPATED: Patients with type 2 diabetes INCLUSION CRITERIA: Between 30 and 75 years, diagnosed within 2 years, treated with one of the following for equal to or more than 3 months to 12 years: once or twice-daily NPH insulin; once daily glargine; once daily or three times daily ultralente insulin or insulin mixture. All patients on immediate or extended release metformin and /or sulfonylurea for at least 3 months prior to screening; or fixed dose sulfonylurea/metformin combination therapy. At time of screening: HbA1c level equal to or less than 10.5; BMI >27 and less than 40kg/m2; history of stable body weight EXISTING THERAPY: insulin and oral agents EXCLUSION CRITERIA: >3 episodes of severe hypoglycaemia within 6 months prior to screening, used any prescription drug to promote weight loss within 3 months, previously received exenatide or GLP-1 analogs NUMBERS: 49 (51 were randomised; 1 discontinued before receiving study drug and 1 withdrawn as found not to have type 2 diabetes) AGE: mean EXEN 54 years (SD 8) and INSULIN 52 (8) DURATION OF DIABETES: mean EXEN 10.4 years (SD 6.2) and INSULIN 11.9 years (SD	INTERVENTION: Exenatide (EXEN), subcutaneous, 10ug/day for 4 weeks and 20ug/day for 12 weeks, before morning and evening meals CONTROL: Usual insulin (INSULIN) regimen for 16 weeks OTHER TREATMENT: Both groups continued oral medication and instructed to continue diet and exercise regimen	PRIMARY OUTCOMES: 1. HbA1c *mean HbA1c (%) change from baseline to 16 weeks 2. Fasting serum glucose *mean fasting serum glucose (mmol/L) at baseline and 16 weeks SECONDARY OUTCOMES: 1. Blood chemistries 2. Fasting serum lipids 3. Fasting C-piptide 4. Body weight *mean change in body weight from baseline to 16 weeks 5. point self-monitored blood glucose OTHER OUTCOMES: 1. Adverse events defined as any untoward medical occurrence, without regard to the possibility of a causal relationship

Study	Methods	Participants	Interventions	Outcomes
		7.4) HbA1c: mean EXEN 8% (SD 1.2) and INSULIN 8.3% (SD 0.9) GENDER: EXEN 46% males and INSULIN 50% males ETHNIC GROUPS: not reported		
DeFronzo 2005	TRIAL DESIGN: RCT DURATION OF INTERVENTION: 30 weeks DURATION OF FOLLOW-UP: 30 weeks RUN-IN PERIOD: 4 weeks single blind with twice daily sc injections of PLACEBO RANDOMISATION PROCEDURE: Stratified according to screening HbA1c values (<9% and equal to or more than 9%) BLINDING: Triple blinded. Except for lead-in period (single blind) and MIN or MAX sulfonylurea dose (not blinded). SETTING: 91 sites (82 De Fronzo at 30 weeks, 54 Ratner at 82 weeks) COUNTRY: US ITT ANALYSIS? Yes DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate SAMPLE SIZE CALCULATION: Yes; powered for primary outcome HbA1c OVERALL RISK OF BIAS: + SOURCE OF FUNDING:	WHO PARTICIPATED: Patients with type 2 diabetes treated with metformin and a sulfonylurea (those taking a sulfonylurea were excluded in De Fronzo) INCLUSION CRITERIA: 22 to 77 years of age (19-78 in De Fronzo), type 2 diabetes, treated with metformin, screening FPG of <13.3 mmol/l, BMI 27 to 45kg/m2, HbA1c 7.5 (7.1 in De Fronzo) to 11%, metformin dose equal to or more than 1500 mg/day for 3 months before screening and sulfonylurea dose at least maximum effective dose for 3 months before screening; weight stable for 3 months before screening, no clinically significant abnormal laboratory test values, females post-menopausal, surgically sterile, or using contraceptives for 3 months before screening and continuing throughout study EXISTING THERAPY: failing metformin EXCLUSION CRITERIA: Use of meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, exogeneous insulin therapy, weight loss drugs, any investigational drug, or evidence of clinicaly significant comorbid conditions NUMBERS: 733 AGE: EXEN10 55 years	INTERVENTION: Exenatide subcutaneous 10ug/day, morning and evening for 30 weeks INTERVENTION: Exenatide subcutaneous 10ug/day for four weeks increasing to 20ug/day for 26 weeks, morning and evening CONTROL: Placebo sc twice daily OTHER TREATMENT: All participants continued current regimen of metformin. No variation of sulfonylurea dose permitted after week 12. Unblinded randomisation to either maximally effective or minimum recommended doses of sulfonylurea	PRIMARY OUTCOMES: 1. HbA1c *mean HbA1c change from baseline 2. Safety Treatment Emergent Adverse events defined as those occurring upon or after receiving the first randomised dose SECONDARY OUTCOMES: 1. HbA1c *Number (%) of patients achieving HbA1c equal to or less than 7% by week 30 (of ITT subjects with baseline HbA1c >7%) Change in HbA1c at 30 weeks stratified by baseline A1c 2. Effect of exenatide on fasting and postprandial (meal cohort only) plasma glucose concentrations 3. Body weight *Change in body weight (kg) from baseline to 30 weeks 4. Fasting and postprandial concentrations of blood insulin 5. fasting proinsulin 6. lipids

Study	Methods	Participants	Interventions	Outcomes
	Amylin Pharmaceuticals and Eli Lilly	SD 9 and EXEN20 55 years SD 10 and PLACEBO 56 years SD 10 DURATION OF DIABETES: EXEN10 8.7 years SD 5.9 and EXEN 20 8.7 years SD 6.1 and PLACEBO 9.4 years SD 6.1 HbA1c: EXEN10 8.5 SD 1 and EXEN20 8.5 SD 1.1 and PLACEBO 8.5 SD 1 GENDER: EXEN10 59.2% males EXEN20 59.3% males and PLACEBO 55.9% males ETHNIC GROUPS: EXEN10 white 69%, black 10.2%, hispanic 15.9% EXEN20 white 66.4%, black 11.6%, hispanic 16.6% PLACEBO white 68.4%, black 12.1%, hispanic 15.8% COMORBIDITIES: COMEDICATIONS: PHARMACONAIIVE:		
Heine 2005	TRIAL DESIGN: Randomised parallel open label DURATION OF INTERVENTION: 26 weeks DURATION OF FOLLOW-UP: 26 weeks RUN-IN PERIOD: RANDOMISATION PROCEDURE: Central randomisation table administered by interactive voice-response system. Randomisation stratified by investigative size (block of 4) BLINDING: Open label SETTING: 82 centres COUNTRY: 13 countries ITT ANALYSIS?: yes	WHO PARTICIPATED: Patients with type 2 diabetes INCLUSION CRITERIA: 30 to 75 years of age, treated with stable and maximally effective doses of metformin and a sulfonylurea for at least 3 months before screening, HbA1c ranging from 7 to 10%, BMI ranging from 25kg/m2 to 45 kg/m2 EXISTING THERAPY: metformin and a sulfonylurea EXCLUSION CRITERIA: had more than 3 episodes of severe hypoglycaemia within 6 months before screening; had been treated with insulin within 3 months before screening, with TZDs, within 4 months before screening, with alpha-glucosidase inhibitors within 3 months before	INTERVENTION: Exenatide (EXEN) 20ug/day, subcutaneous, morning and evening CONTROL: Insulin Glargine (INSULIN), subcutaneous, titrated to BG level <5.6mmol/l OTHER TREATMENT: Metformin and sulfonylurea fixed at prestudy levels	PRIMARY OUTCOMES: 1. HbA1c *mean HbA1c change from baseline to 26 weeks *% patients who achieved target HbA1c level equal to or less than 7% (for ITT patients with HbA1c level >7% at baseline) SECONDARY OUTCOMES: 1. Body weight *mean change in body weight from baseline to 26 weeks 2. Fasting plasma glucose *Reduction in fasting plasma glucose from baseline to 26 weeks *% of patients

Study	Methods	Participants	Interventions	Outcomes
	DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate SAMPLE SIZE CALCULATION: Yes, powered for primary outcome HbA1c OVERALL RISK OF BIAS: ++ SOURCE OF FUNDING: Eli Lilly and Amylin Pharmaceuticals	screening, or with meglitinides within 3 months before screening NUMBERS: 551 AGE: EXEN 55 INSULIN 56.6 DURATION OF DIABETES: HbA1c: EXEN 8.2% SD 1 and INSULIN 8.3% SD 1 GENDER: EXEN 55% males INSULIN 56.5 males ETHNIC GROUPS: EXEN white 79.8%, black 0.7%, hispanic 15.6% INSULIN white 80.5%, black 1.1%, hispanic 15%		achieving fasting plasma glucose <5.6 mmol/l 3. Blood glucose *Mean change in self-monitored blood glucose from baseline to 26 weeks 4. Patient-reported health outcome measures (Secnik Boye)
Kendall 2005	TRIAL DESIGN: RCT double blind parallel DURATION OF INTERVENTION: 30 weeks DURATION OF FOLLOW-UP: 30 weeks RUN-IN PERIOD: 4 weeks RANDOMISATION PROCEDURE: Randomisation stratified according to HbA1c values. No details reported BLINDING: Double blind SETTING: 91 centres COUNTRY: US ITT ANALYSIS?: yes DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate SAMPLE SIZE CALCULATION: Yes, powered for primary outcome HbA1c OVERALL RISK OF BIAS: + SOURCE OF FUNDING:	WHO PARTICIPATED: Patients with type 2 diabetes treated with metformin and sulfonylurea INCLUSION CRITERIA: 22 to 77 years of age, screening DPG <13.3mmol/l; BMI 27 to 45 kg/m2; HbA1c 7.5 to 11%. Metformin dose was eual to or more than 1500mg/day and sulfonyluea dose at least max effective dose for 3 months before screening. Weight stable for 3 months before screening; no clinically significant abnormal lab test values (>25% outside normal lab values). Female subjects postmenopausal, surgically sterile, or using contraceptives for 3 months before screening and continuing through study EXISTING THERAPY: metformin and a sulfonylurea EXCLUSION CRITERIA: Use of meglitinides, thiazolidinediones, alpha glucosidase inhibitors, exogenous insulin therapy, weight loss drugs, corticosteroids, drugs known to affect GI	INTERVENTION: Exenatide (EXEN10) 10ug/day, subcutaneous, morning and evening INTERVENTION: Exenatide (EXEN20) 20ug/day, subcutaneous, morning and evening CONTROL, subcutaneous, titrated to BG level <5.6mmol/l OTHER TREATMENT: Metformin and sulfonylurea fixed at prestudy levels	PRIMARY OUTCOMES: 1. HbA1c *mean HbA1c change from baseline to 30 weeks *% patients who achieved target HbA1c level equal to or less than 7% (for ITT patients with HbA1c level >7% at baseline) SECONDARY OUTCOMES: 1. Body weight *mean change in body weight from baseline to 30 weeks 2. Fasting plasma glucose *Reduction in fasting plasma glucose from baseline to 30 weeks *% of patients achieving fasting plasma glucose <5.6 mmol/l 3. Blood glucose *Mean change in self-monitored blood glucose from baseline to 26 weeks 4. Fasting

Study	Methods	Participants	Interventions	Outcomes
	Amylin Pharmaceuticals and Eli Lilly	motility, transplantation medications or any investigational drug or evidence of clinically significant co-morbid conditions for 3 months before screening DIAGNOSTIC CRITERIA: not reported NUMBERS: 733 AGE: EXEN10ug 55 years SD9 and EXEN20ug 55 years SD10 and PLACEBO 56 years SD10 DURATION OF DIABETES: EXEN10ug 8.7 years SD 5.9 and EXEN20ug 8.7 years SD 6.4 and PLACEBO 9.4 years SD 6.2 HbA1c: EXEN10ug 8.5% SD 1 and EXEN20ug 8.5% SD 1.1 and PLACEBO 8.5% SD1 GENDER: EXEN10ug 59.2% males and EXEN20ug 59.3% males and PLACEBO 55.9% males ETHNIC GROUPS: EXEN10ug white 69%, black 10.2%, hispanic 15.9% and EXEN20ug white 66.4%, black 11.6%, hispanic 16.6% and PLACEBO 68.4%, black 12.1%, hispanic 15.8%		plasma lipids 5. Exenatide pharmacokinetics ADDITIONAL PUBLISHED OUTCOMES: Safety 1. Treatment emergent adverse events 2. Hypoglycaemic events 3. Clinical laboratory tests 4. Physical examination 5. 12 lead ECG 6. Vital signs 7. Titreing of anti-exenatide antibodies
Nauck 2007	TRIAL DESIGN: RCT DURATION OF INTERVENTION: 52 weeks DURATION OF FOLLOW-UP: 52 weeks RUN-IN PERIOD: RANDOMISATION PROCEDURE: Procedure not reported. Stratified by site based on screening values of HbA1c BLINDING: not reported SETTING: multicentre (number not	WHO PARTICIPATED:Patients with type 2 diabetes INCLUSION CRITERIA: bewteen 30 and 75 years of age; had suboptimal glycaemic control despite receiving optimally effective metformin and sulfonylurea therapy for at least 3 months; HbA1c levels equal to or more than 7 and equal to or less than 11%; BMI equal to or greater than 25 and equal to or less than 40 kg/m2 and a history of stable body weight EXISTING THERAPY:	INTERVENTION: EXENATIDE, subcutaneous, 10ug/day for 4 weeks then 20ug for 48 weeks (morning and evening doses) CONTROL: INSULIN ASPART 30/70, subcutaneous, morning and evening doses OTHER TREATMENT: Maintenance of optimally effective prestudy metformin and	PRIMARY OUTCOMES: 1. HbA1c *Mean change in HbA1c from baseline to week 52 SECONDARY OUTCOMES 1. Body weight *Mean reduction in body weight from baseline to week 52 2. Fasting serum glucose *Mean change in fasting serum glucose from baseline to week 52

Study	Methods	Participants	Interventions	Outcomes
	reported) COUNTRY: 13 countries ITT ANALYSIS: yes DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: yes SAMPLE SIZE CALCULATION: yes OVERALL RISK OF BIAS: ++ SOURCE OF FUNDING: Not specified but authors declared as consultants or employees of Amylin Pharmaceuticals and/or Eli Lilly	metformin and sulfonylurea EXCLUSION CRITERIA: more than 3 episodes of severe hypoglycaemia within 6 months prior to screening, had been treated with insulin, TZDs, alpha-glucosidase inhibitors or meglitinides for longer than 2 weeks within 3 months NUMBERS: 501 in ITT sample AGE: EXEN 59 years SD9 and INSULIN 58 SD9 DURATION OF DIABETES: EXEN 9.8 years SD 6.3 and INSULIN 10 years SD 6.2 HbA1c: EXEN 8.6% SD1 and INSULIN 8.6 SD1.1 GENDER: EXEN 53% males and INSULIN 49% males ETHNIC GROUPS: not reported	sulfonylurea doses	3. SMBG 4. Beta cell function *mean change in beta cell function from baseline to 52 weeks (HOMA-B) 5. Insulin sensitivity *mean change in insulin sensitivity from baseline to 52 weeks (HOMA-S) 6. HDL cholesterol and fasting lipids OTHER OUTCOMES 1. Treatment emergent adverse events
Zinman 2007	TRIAL DESIGN: RCT DURATION OF INTERVENTION: 16 weeks DURATION OF FOLLOW-UP:16 weeks RUN-IN PERIOD: 2 week single blind placebo run-in RANDOMISATION PROCEDURE: Central randomisation table; automated interactive voice-response system administered assignment; stratified by site and current treatment (TZD alone or TZD plus metformin) BLINDING: Double-blind. Prefilled disposable injection pens or	WHO PARTICIPATED: Patients with type 2 diabetes INCLUSION CRITERIA: Adults; treated with stable dose of TZD for at least 4 months before screening; patients received TZD therapy alone or in combination with a stable dosage of metformin for 30 days; HbA1c value between 7.1% and 10% at screening; BMI between 25kg/m2 and 45kg/m2, and a history of stable body weight (equal to or less than 10% variation) for at least 3 months before screening EXISTING THERAPY: TZD alone or TZD with metformin EXCLUSION CRITERIA: not reported NUMBERS: 233 AGE: EXEN 55.6 years SD10.8 and PLACEBO 56.6 years SD 10.2 DURATION OF	INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Exenatide (EXEN), subcutaneous, 10ug/day for 4 weeks and 20ug/day for 12 weeks, morning and evening doses CONTROL (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Placebo (PLACEBO), subcutaneous, morning and evening doses OTHER TREATMENT: Doses of TZD and metformin constant throughout study	PRIMARY OUTCOMES: Changes HbA1c *Mean reduction in HbA1c from baseline to 16 weeks *% of patients who achieved a target HbA1c level equal to or less than 7% (of those patients with HbA1c level >7% at baseline) *% of patients who achieved a target HbA1c level equal to or less than 6.5% SECONDARY OUTCOMES: 1.Body weight *Mean reduction in body weight from baseline to 16 weeks 2. Fasting serum glucose *Mean reduction in fasting serum

Study	Methods	Participants	Interventions	Outcomes
	cartridges containing indistinguishable Exenatide and placebo solutions used. SETTING: 49 research clinics, hospitals and primary facilities COUNTRY: USA, Canada, Spain ITT ANALYSIS? Yes DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Yes SAMPLE SIZE CALCULATION: Yes OVERALL RISK OF BIAS: ++ SOURCE OF FUNDING: Eli Lilly and Amylin Pharmaceuticals	DIABETES: EXEN 7.3 years SD 4.9 and PLACEBO 8.2 years SD 5.8 HbA1c: EXEN 7.9% SD 0.9 and PLACEBO 7.9 SD 0.8 GENDER: EXEN 53.7% males and PLACEBO 57.1% males ETHNIC GROUPS: EXEN white 85.1% and PLACEBO white 82.!%		glucose from baseline to 16 weeks 3. SMBG 4. HOMA levels

1.2 Results by key outcomes

Effect on HbAc1

Study	Study Arm and Number randomised	HbA1c (%) baseline	Change from baseline (%)	P value from baseline	Difference between groups at end (Exenatide-Comparator 95% CI)	P value between groups	% Patients achieving HbA1c of ≤ 7%
Barnett 2007 (cross –over trial)	Exenatide/ Insulin glargine treatment sequence + MET or SU (n=68)	8.89 (SE 0.13)	-1.36 (SE 0.09)	P<0.001		NS	37.5% (Exenatide treated pts)
	Insulin/glargine/Exenatide treatment sequence + MET or SU (n=70)	9.00 (SE 0.13)	-1.36 (SE 0.09)	P<0.001			39.8% (glargine treated pts)
Davis 2007	Exenatide + oral medications (n= 33)	8.0 (SD 1.2)	+0.3 (SE 1.5)	NS	0.4%	NS	
	Current Insulin regimen + oral medications (n=16)	8.3 (SD (0.9)	-0.1 (SE 0.7)	NS			
DeFronzo 2005	Exenatide (10 µg) + MET (n=113)	8.18 (SD 1.0)	-0.78 (SE 0.1)			P<0.002	46%
	Placebo + MET (n=113)	8.2 (SD 1.0)	+0.08 (SE 0.1)				13%
Heine 2005	Exenatide + MET + SU(n= 282)	8.18	-1.11		0.017 (-0.123 to 0.157)	NS	46%
	Insulin glargine + MET + SU (n=267)	8.23	-1.11				48%
Kendall 2005	Exenatide + MET + SU 5 ug (n=245)	8.5 (SD 1.0)	-0.55 (SE 0.07)			P<0.0001	24% [1]
	Exenatide + MET + SU 10 ug (n=241)	8.5 (SD 1.1)	-0.77 (SE 0.08)				30% [1]
	Placebo + MET + SU (n=247)	8.5 (SD 1.0)	+0.23 (SE 0.07)				7% [1]
Nauck 2007	Exenatide + MET + SU (n=253)	8.6 (SD 1.0)	-1.04 (SE 0.07)	P<0.001	-0.15 (-0.32 to 0.01)	NS (P=0.067)	32% [2]
	Biphasic insulin aspart + MET + SU	8.6 (SD	-0.89 (SE	P<0.001			24% [2]

Study	Study Arm and Number randomised	HbA1c (%) baseline	Change from baseline (%)	P value from baseline	Difference between groups at end (Exenatide-Comparator 95% CI)	P value between groups	% Patients achieving HbA1c of ≤ 7%
	(n=248)	1.1)	0.06)				
Zinman 2007	Exenatide + MET + TZD (n=121)	7.89 (SE 0.9)	-0.89		-0.98 (-1.21 to -0.74)	P<0.001	62% [3] 30% [4]
	Placebo + MET + TZD (n=112)	7.91 (SE 0.8)	+0.09				30% [3] 8% [4]
	MET + glimepiride (n=						
	Insulin glargine MET + glimepiride (n=						

1 For ITT patients with HbA1c level >7% at baseline
2 Accounting for HbA1c stratification at screening
3 For the per protocol sample, with HbA1c level >7% at baseline
4 For the per protocol sample who achieved a target HbA1c level ≤ 6.5% (with HbA1c level >7% at baseline)

Effect on hypoglycaemia

Study	Study Arm and Number	Incidence of hypoglycaemia % (n)	Overall hypoglycaemia rates (events/patient year)	Serious hypoglycaemia	Nocturnal hypoglycaemia	Daytime hypoglycaemia	Severe hypoglycaemia
Barnett 2007 (cross –over trial)	Exenatide + MET or SU	14.7%	1.9 [95% CI, 1.5-2.4]		0.4 event/ patient-year [95% CI, 0.2-0.7]		0 episodes
	Insulin glargine + MET or SU	25.2%	2.6 [95% CI, 2.2-3.2]		1.3 events/patient year [95% CI, 1.0-1.7]		8 episodes
Davis 2007	Exenatide + oral medications (n= 33)	39% (13)	1.72	0		11/13	1 patient treated with exenatide + SU had 3 severe hypos
	Current insulin regimen + oral	38% (6)	0.97	0		4/6	

Study	Study Arm and Number	Incidence of hypoglycaemia % (n)	Overall hypoglycaemia rates (events/patient year)	Serious hypoglycaemia	Nocturnal hypoglycaemia	Daytime hypoglycaemia	Severe hypoglycaemia
	medications (n=16)						
DeFronzo 2005	Exenatide (10 µg) + MET (n=113)	5.3%					0
	Placebo + MET (n=113)	5.3%					0
Heine 2005	Exenatide + MET + SU(n= 282)		7.3 [1]		0.9 event patient year [2]	6.6 event patient year [3]	4 pts
	Insulin glargine + MET + SU (n=267)		6.3		2.4 event patient year	3.9 event patient year	4 pts
Kendall 2005	Exenatide + MET + SU 5 ug (n=245)	19.2% (47)		1 case			
	Exenatide + MET + SU 10 ug (n=241)	27.8% (67)					
	Placebo + MET + SU (n=247)	12.6% (31)					
Nauck 2007	Exenatide + MET + SU (n=253)		4.7 (SE 0.7)		17% (44) [4]		
	Biphasic insulin aspart + MET + SU (n=248)		5.6 (SE 0.7)		25% (62)		
Zinman 2007	Exenatide + MET + TZD (n=121)	10.7% (13)[5]					0
	Placebo + MET + TZD (n=112)	7.1% (8)					0

1 Difference (Exenatide – glargine arms) = 1.1 (CI, -1.3 to 3.4) NS
2 Difference (Exenatide – glargine arms) = -1.6 (CI, -2.3 to -0.9)

3 Difference (Exenatide – glargine arms) = 2.7 (CI, 0.4 to 4.9)
4 p<0.038
5 Difference between groups, 3.6% [CI, -4.6 to 11.8%]

Effect on weight

Study	Study Arm and Number randomised	Weight in kg (SD) at baseline	Change in kg (SE) from baseline	P value from baseline	Difference in kg between groups at end (Exenatide-Comparator 95% CI)	P value between groups
Barnett 2007 (cross –over trial)	Exenatide/ Insulin glargine treatment sequence + MET or SU (n=68)	85.6 (SE 2.0)	Exenatide treated -1.6 [SE 0.3]		-2.2 [SE 0.3] 95% CI, -2.8 to -1.7;	P<0.001
	Insulin/glargine/Exenatide treatment sequence + MET or SU (n=70)	84.0 (SE 2.0)	Glargine treated +0.6 [SE 0.3]			
Davis 2007	Exenatide + oral medications (n= 33)	95 (17)	-4.2 (3)	p<0.001		P < 0.001
	Current insulin regimen + oral medications (n=16)	102 (19)	+0.5 (1.7)	p = NS		
DeFronzo 2005	Exenatide (10 µg) + MET (n=113)	101 (SE 2)	-2.8 (SE 0.5)			P ≤ 0.001
	Placebo + MET (n=113)	100 (SE 2)	-0.3 (SE 0.3)			
Heine 2005	Exenatide + MET + SU(n= 282)	87.5 (16.9)	-2.3		-4.1 (-4.6 to -3.5)	P < 0.0001
	Insulin glargine + MET + SU (n=267)	88.3 (17.9)	+1.8			
Kendall 2005	Exenatide + MET + SU 5 ug (n=245)	97 (19)	-1.6 (0.2)			P ≤ 0.01 vs placebo
	Exenatide + MET + SU 10 ug (n=241)	98 (21)	-1.6 (0.2)			
	Placebo + MET + SU (n=247)	99 (19)	-0.9 (0.2)			
Nauck 2007	Exenatide + MET + SU (n=253)	85.5 (15.7)	-2.5 (0.2)	P <0.01	-5.4 (-5.9 to -5.0)	P <0.001
	Biphasic insulin aspart + MET + SU (n=248)	83.4 (15.6)	-2.9 (0.2)	P <0.01		
Zinman 2007	Exenatide + MET + TZD (n=121)	97.5 (18.8)	-1.75		-1.51 (-2.15 to -0.88)	P <0.001
	Placebo + MET + TZD (n=112)	96.9 (19)	-0.24			

Most frequent side effects

Study	Study Arm and Number randomised	Nausea	Vomiting	Diarrhoea	Any Adverse Event	Discontinuation due to adverse events
Barnett 2007 (cross –over trial)	Exenatide treatment	42.6%	9.6%		65.4%	11
	Insulin glargine treatment	3.1%	3.1%		52.8%	1
Davis 2007	Exenatide + oral medications (n= 33)	48.5%			79%	5 pts
	Current insulin regimen + oral medications (n=16)	12.5%			56%	0 pts
DeFronzo 2005	Exenatide (10 µg) + MET (n=113)	45%	12%	16%	2.7% (serious) 9.7% (severe)	7.1%
	Placebo + MET (n=113)	23%	4%	8%	3.5% (serious) 8.8% (severe)	0.9%
Heine 2005	Exenatide + MET + SU (n= 282)	161 (57.1%) *	49 (17.4%) *	24 (8.5%)**		9.5%
	Insulin glargine + MET + SU (n=267)	23 (8.6%)	10 (3.7%)	8 (3.0%)		0.7%
Kendall 2005	Exenatide + MET + SU 5 ug (n=245)	96 (39.2%)	36 (14.7%)	25 (10.2)		14 (5.7%)
	Exenatide + MET + SU 10 ug (n=241)	117 (48.5%)	33 (13.7%)	42 (17.4)		22 (9.1%)
	Placebo + MET + SU (n=247)	51 (20.6%)	11 (4.5%)	16 (6.5%)		11 (4.5%)
Nauck 2007	Exenatide + MET + SU (n=253)	84 (33.2%)	38 (15.0%)	24 (9.5%)	179 (70.8%)	Together, 5.1% of patients withdrew because of gastrointestinal-related adverse events
	Biphasic insulin aspart + MET + SU (n=248)	1 (0.4%)	8 (3.2%)	5 (2.0%)	123 (49.6%)	
Zinman 2007	Exenatide + MET + TZD (n=121)	48 (39.7%)[1]	16 (13.2%)[2]	7 (5.8%)[3]	92 (76.0%) pts reporting ≥ 1 AE)	19 (16%)
	Placebo + MET + TZD (n=112)	17 (15.2%)	1 (0.9%)	3 (2.7%)	73 (65.2%) pts reporting ≥ 1 AE)	2 (2%)

** p <0.001 compared to insulin glargine arm ** p 0.006 compared to insulin glargine arm*
1 The between-group difference in % of patients (exenatide minus placebo) was 24.5 % (CI, 12.7 to 36.3%)
2 The between-group difference in % of patients (exenatide minus placebo) was 12.3 % (CI, 5.2 to 19.5 %).
3 The between-group difference in % of patients (exenatide minus placebo) was 3.1 % (CI, -2.9 to 9.1 %).

1.3 Included studies for the DPPIV inhibitor evidence review

Description of studies

Study	Methods	Participants	Interventions	Outcomes
Bolli 2008	TRIAL DESIGN: RCT DURATION OF INTERVENTION: 24 weeks DURATION OF FOLLOW-UP: 24 weeks RUN-IN PERIOD: None reported RANDOMISATION PROCEDURE: Not reported BLINDING: Reported as 'double-blind' SETTING: Not clear COUNTRY: Multinational – Germany, UK, USA, Spain, Italy, Switzerland, Austria, South Africa, Australia ITT ANALYSIS? No, per-protocol analysis DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate SAMPLE SIZE CALCULATION: Yes, and adequately powered per-protocol OVERALL RISK OF BIAS: + SOURCE OF FUNDING: Novartis	WHO PARTICIPATED: Patients with type 2 diabetes inadequately controlled with prior metformin monotherapy INCLUSION CRITERIA: 18 to 77 years of age, type 2 diabetes, treated with metformin≥1500mg per day, screening HbA1 7.5-11.0%, non-fertile or using a medically approved birth control method, BMI 22 to 45kg/m2, FPG<15mmol/l EXISTING THERAPY: failing metformin EXCLUSION CRITERIA: History of type 1 diabetes or secondary forms of diabetes, acute metabolic diabetic complications. myocardial infarction. unstable angina or coronary artery bypass surgery within the previous 6 months, congestive heart failure (NYHA I-IV) and liver disease such as cirrhosis or chronic active hepatitis. Also specific abnormal lab. NUMBERS: 576 randomised AGE: Vilda100mg+met 56.3 years SD 9.3 and pio30mg+met 57.0 years SD 9.7 DURATION OF DIABETES: Vilda100mg+met 6.4 years SD 4.9 and pio30mg+met 6.4 years SD 5.2 HbA1c: Vilda100mg+met 8.4% SD 1.0 and pio30mg+met 8.4% SD 0.9 GENDER: Vilda100mg+met 61.7% males and pio30mg+met 64.1% males ETHNIC GROUPS: Vilda100mg+met white 82.4%, hispanic or latino 8.5% asian (non-indian subcontinent) 4.1% black 3.0% others 2.0% pio30mg+met white 81.9%, hispanic or latino 10.3% asian (non-indian subcontinent) 3.9% black 2.5% others 1.4% COMORBIDITIES: not reported	INTERVENTION: vildagliptin 100mg daily, two equally divided doses CONTROL: pioglitazone 30mg once daily OTHER TREATMENT: Assumed that participants continued current regimen of metformin.	PRIMARY OUTCOMES: 1. HbA1c *mean HbA1c change from baseline 2. Percentage of patients responsive to treatment (HbA1c<7%, ≤6.5%, reduction ≥1%, ≥0.7%, ≥0.5%, meeting at least one criteria) SECONDARY OUTCOMES: 1. FPG 2. Fasting lipids 3. Body weight *Change in body weight (kg) from baseline to 24 weeks Safety

Study	Methods	Participants	Interventions	Outcomes
		COMEDICATIONS: not reported		
Hermansen 2007	TRIAL DESIGN: RCT DURATION OF INTERVENTION: 24 weeks DURATION OF FOLLOW-UP: 24 weeks RUN-IN PERIOD: upto 14 weeks RANDOMISATION PROCEDURE: Not reported but 1:1 BLINDING: Reported a s 'double-blind' SETTING: Not clear COUNTRY: reported as 'multinational' ITT ANALYSIS? Yes, with LOCF DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate SAMPLE SIZE CALCULATION: Yes, but not reported if numbers achieved OVERALL RISK OF BIAS: + SOURCE OF FUNDING: Merck	WHO PARTICIPATED: Patients with type 2 diabetes INCLUSION CRITERIA: 18 to 75 years of age, type 2 diabetes, taking either glimepiride (any dose) alone or in combination with metformin (any dose), or taking another oral hypoglycaemic drug mono-dual-or triple therapy or not taking any oral hypoglycaemic drug during the previous 8 weeks EXISTING THERAPY: If taking glimepiride alone or with metformin, entered placebo run-in. If other regime and depending on HbA1c control, discontinued and started treatment with glimepiride alone or with metformin, dose titrated for 4 weeks, then run-in period 10 weeks, with placebo run-in period if HbA1c ≥7.5% and ≤ 10.5%. Entered for randomization if adherence ≥75% EXCLUSION CRITERIA: History of type 1 diabetes, treated with insulin in prior 8 weeks, renal dysfunction, history of hypersensitivity, intolerance or contraindications to glimepiride, sulphonylureas, metformin or pioglitazone. NUMBERS: 441 randomised - sit100mg+MET+SU 116 placebo+MET+SU 113 AGE: sit100mg+MET+SU 56.5 years SD 9.6 and placebo+MET+SU 57.7 years SD 8.9 DURATION OF DIABETES: sit100mg+MET+SU 9.3 years SD 5.7 and placebo+MET+SU 10.6 years SD 6.8 HbA1c: sit100mg+MET+SU 8.27% SD 0.73 and placebo+MET+SU 8.26% SD 0.68 GENDER: sit100mg+MET+SU 52.6% males and placebo+MET+SU 59% males ETHNIC GROUPS: sit100mg+MET+SU white 64.7%, black 6.6% hispanic 24.5% asian 5.7% others 5.7% placebo+MET+SU white 71.7%,	INTERVENTION: sitagliptin 100mg once daily CONTROL: placebo OTHER TREATMENT: Continued stable doses of glimepiride and metformin (as established in the run-in period). Also given rescue therapy of pioglitazone 30mg/day (open label) if FPG not meeting specific, and progressively lower goals after randomization. Discontinued from study if rescue therapy for more than 4 weeks and FPG still high. NOTE: Only reported details for relevant comparator arms	PRIMARY OUTCOMES: 1. HbA1c *mean HbA1c change from baseline. If significant then assessed treatment effects by strata SECONDARY OUTCOMES: 1. FPG 2. Fasting lipids – TC, LDL-C, TG, HDL-C 3. Beta cell function 4. Changes in insulin resistance Safety and tolerability

Study	Methods	Participants	Interventions	Outcomes
		black 8.0% hispanic 6.2% asian 11.5% others 2.7% COMORBIDITIES: not reported COMEDICATIONS: not reported		
Nauck 2007	TRIAL DESIGN: RCT DURATION OF INTERVENTION: 52 weeks DURATION OF FOLLOW-UP: 52 weeks RUN-IN PERIOD: 2 week single-blind PLACEBO RANDOMISATION PROCEDURE: Not reported, 1:1 ratio BLINDING: Double blinded. Except for lead-in period (single blind) SETTING: Not clear COUNTRY: Described as 'multinational' ITT ANALYSIS? Per-protocol and all-patients treated analysis DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate SAMPLE SIZE CALCULATION: Not reported OVERALL RISK OF BIAS: - SOURCE OF FUNDING: Merck	WHO PARTICIPATED: Patients with type 2 with inadequate control on metformin INCLUSION CRITERIA: 18-78 years of age, type 2 diabetes, treated with metformin (eligible if not taking any oral therapy, any oral therapy as monotherapy, any oral therapy with metformin, then titrated to METFORMIN monotherapy over 8 week period) EXISTING THERAPY: failing metformin EXCLUSION CRITERIA: History of type 1 diabetes, insulin use within 8 weeks of screening, renal function impairment inconsistent with use of metformin, FPG at or prior to randomization>15.0mmol/l NUMBERS: 1172 randomised AGE: SIT+MET 56.8 (SD9.3) and SU+MET 56.6 (SD9.8) years DURATION OF DIABETES: SIT+MET 6.5 years (SD6.1) and SU+MET 6.2years (SD5.4) HbA1c: SIT+MET 7.7 (SD0.9)and SU+MET 7.6 (SD0.9) GENDER: SIT+MET 57.1% males SU+MET 61.3% ETHNIC GROUPS: SIT+MET white 73.5%, black 7.0%, hispanic 7.3%, asian 8.5%, other 3.7% SU+MET white 74.3%, black 6.0%, hispanic 739%, asian 8.4%, other 3.4% COMORBIDITIES: Not reported COMEDICATIONS: Allowed lipid lowering, antihypertensive, thyroid, medications and HRT, birth control – but expected to remain at stable doses. Other treatments for hyperglycaemia not allowed. PHARMACONAIIVE: SIT+MET 4.3% and	INTERVENTION: sitagliptin 100mg once daily CONTROL: glipizide, initial dose of 5mg with uptitration according to protocol specifications to max of 20mg/day OTHER TREATMENT: Assumed that all participants continued stable regimen of metformin.	PRIMARY OUTCOMES: 1. HbA1c *mean HbA1c change from baseline SECONDARY OUTCOMES: 1. HbA1c *Number (%) of patients achieving HbA1c equal to or less than 7% or 6.5% Change in HbA1c stratified by baseline A1c Safety and tolerability Adverse experiences, lab safety parameters, body weight, vital signs, ECG data Compliance tablet count

Study	Methods	Participants	Interventions	Outcomes
		SU+MET 4.8% at screening		
Scott 2007	TRIAL DESIGN: RCT DURATION OF INTERVENTION: 18 weeks DURATION OF FOLLOW-UP: 18 weeks RUN-IN PERIOD: 2 week single-blind PLACEBO RANDOMISATION PROCEDURE: Not reported, 1:1:1 ratio BLINDING: Double blinded. Except for lead-in period (single blind) SETTING: Not clear COUNTRY: Described as 'multinational' ITT ANALYSIS? All patients treated analysis DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate SAMPLE SIZE CALCULATION: Not reported OVERALL RISK OF BIAS: + SOURCE OF FUNDING: Merck	WHO PARTICIPATED: Patients with type 2 diabetes treated with metformin INCLUSION CRITERIA: 18 to 75 years of age, type 2 diabetes, treated with metformin at stable dose of at least 1500mg/day for at least 10 weeks prior to screening, HbA1c 7 to 11% EXISTING THERAPY: failing metformin EXCLUSION CRITERIA: Type 1 diabetes, insulin use within 8 weeks of screening, impaired renal function, contraindications for TZDs or metformin. NUMBERS: 273 randomised AGE: SIT100 55.2 years SD 9.8 and ROSI8 54.8 years SD 10.5 and PLACEBO 55.3 years SD 9.3 DURATION OF DIABETES: SIT100 4.9 years SD 3.5 and ROSI8 4.6 years SD 4.0 and PLACEBO 5.4 years SD 3.7 HbA1c: SIT100 7.8 SD 1.0 and ROSI8 737 SD 0.8 and PLACEBO 7.7 SD 0.9 GENDER: SIT100 55% males ROSI8 63% males and PLACEBO 59% males ETHNIC GROUPS: SIT100 caucasian 61%, asian 38%, others 1% ROSI8 caucasian 59%, asian 38%, others 3% PLACEBO caucasian 61%, asian 39%, others 0% COMORBIDITIES: 59% hypertension, 42% hyperlididaemia/dyslipidaemia COMEDICATIONS: Not reported PHARMACONAIIVE:N/A	INTERVENTION: sitagliptin 100mg once daily INTERVENTION: rosiglitazone 8,g once daily CONTROL: Placebo once daily OTHER TREATMENT: All participants continued current regimen of metformin. All patients received counseling on exercise and a weight maintaining diet	PRIMARY OUTCOMES: 1. HbA1c *mean HbA1c change from baseline 2. Beta-cell function Proinsulin/insulin ratio and HOMA-beta 3. Meal tolerance test SECONDARY OUTCOMES: 1. Adverse experiences 2. Physical examinations 3. Vital signs 4. Body weight

1.4 Results by key outcomes

Effect on HbAc1

Study	Study Arm	HbA1c (%) baseline	HbA1c (%) End	Change from baseline (%)	Difference between groups at end (DPP 4 inhibitor-Comparator)	P value between groups	% achieving Hba1c <7%
Bolli 2008	Vildagliptin + metformin	8.4%		- 0.88% (+/- 0.5%*)	0.10% (95% CI – 0.05 to -0.26)		27%
	Pioglitazone + metformin	8.4%		- 0.98% (+/-0.06%*)			36%
Hermansen 2007	Sitagliptin + metformin + glimepiride	8.27%		-0.59%	-0.89	<0.001	22.6%
	Metformin + glimepiride	8.26%		+ 0.30%			1.0%
Nauck 2007 (per protocol)	Sitagliptin + metformin	7.48%	6.84%	-0.67%	-0.01% (95%CI -0.09 to 0.08)		63%
	Glipizide + metformin	7.52%	6.86%	-0.67%			59%
Scott 2007	Sitagliptin + metformin	7.8%	7.01%	- 0.79%	+ 0.07	NS	55%
	Rosiglitazone + metformin	7.7%	6.94%	- 0.76%			63%

** as reported by authors. The different sized SEs look odd. It may be the 0.5% for the vildagliptin group which is wrong – it looks that way from the graph of HbA1c in the paper. It should perhaps be 0.05%?*

Effect on weight

Study	Study arm	BMI baseline	Weight – kg (SD) baseline	Change from baseline (%)	Difference between groups at end (DPP4 inhibitor-Comparator)	P value between groups
Bolli 2008	Vildagliptin + metformin	32.2	91.8 (18.5)	0.3kg	-1.6kg	< 0.001
	Pioglitazone + metformin	32.1	91.2 (16.9)	1.9kg		
Hermansen 2007	Sitagliptin + metformin + glimepiride	31.3	87.2 (19.7)	+ 0.4kg	+ 1.1 kg	

Study	Study arm	BMI baseline	Weight – kg (SD) baseline	Change from baseline (%)	Difference between groups at end (DPP4 inhibitor-Comparator)	P value between groups
	Metformin + glimepiride	30.7	86.7 (21.1)	- 0.7kg		
Nauck 2007 (per protocol)	Sitagliptin + metformin	31.2 (all randomised)	89.5 (17.4) (all randomised)	-1.5kg	-2.5kg (95%CI -3.1 to -2.0)	<0.001
	Glipizide + metformin	31.3 (all randomised)	89.7 (17.5) (all randomised)	1.1kg		
Scott 2007	Sitagliptin + metformin	30.3	83.1 (17.1)	- 0.4kg	- 1.9kg (95% CI 1.3 to 2.5)	
	Rosiglitazone + metformin	30.4	84.9 (18.5)	+1.5kg		

Most frequent side effects

Study		Nausea	Vomiting	Diarrhoea	Other GI	Any AE	Discontinuation because of SE
Bolli 2008	Vildagliptin + metformin	NR	NR	3.4%	3.1% (constipation)	2.0%	3.1%
	Pioglitazone + metformin	NR	NR	2.9%	1.1 % (constipation)	4.6%	3.2%
Hermansen 2007	Sitagliptin + metformin + glimepiride	0.9%	1.7% (2 patients ex 116)	0.9%	All GI AEs 4.3%	18%	1.7%
	Metformin + glimepiride	0.9%	0.9% (1 patient ex 113)	3.5%	All GI AEs 7.1%	7.1%	1.8%
Nauck 2007 (all patients treated)	Sitagliptin + metformin	2.6%	0.9%	5.8%	NR	71.3%	2.7% 1.4% drug related
	Glipizide + metformin	2.7%	1.5%	5.5%	NR	76.0%	3.6% 1.4% drug related
Scott 2007	Sitagliptin + metformin	1%	1%	3%	Any GI 9%	39%	2%
	Rosiglitazone + metformin	1%	1%	3%	Any GI 7%	44%	0%

1.5 Included studies for the long-acting insulin analogues evidence review

Description of reviews

Review	Inclusion criteria and methodology	Included studies	Quality
Duckworth 2007 focus: clinical evidence for insulin glargine versus NPH insulin funding: industrial (Sanofi-Aventis USA)	INCLUSION CRITERIA study design: not specified participants: patients with type 2 diabetes interventions: insulin glargine versus NPH insulin outcomes: HbA1c, FPG, incidence of hypoglycaemia, other safety assessments METHODOLOGY search strategy: Pubmed 1996 to 2005; search terms reported; English language only study selection: not described quality assessment: not described data extraction: not described meta-analysis: no data analysis: not described subgroups / sensitivity analyses: none	number of included trials: 8 number of participants: 3379 (range 100 to 756) TRIALS: design: all open-label randomised controlled trials duration: 4 weeks to 1 year quality: not reported origin: not reported funding: many of the included trials supported by Sanofi-Aventis (no further details) PARTICIPANTS: age: not reported gender: not reported BMI: not reported diabetes duration: not reported HbA1c: mean 8.5 to 9.7% previous medication: see below, some limited details given INTERVENTIONS: 2 trials in patients with previous insulin therapy; 5 trials in insulin-naïve patients on oral therapy; 1 trial included patients on oral therapy plus insulin; dose titration targets 80 to 140 mg/dL (4.5 to 7.8 mmol/L) in 2 trials, 72 to 126 mg/dL (4 to 7 mmol/L) in 1 trial, 120 mg/dL (6.7 mmol/L) in 2 trials, ≤100 mg/dL (5.6 mmol/L) in 3 trials; in trials with previous oral agents: 4 trials continued existing oral therapy, in 1 trial existing oral therapy was replaced by 3 mg glimepiride, in 1 trial fixed dose of 2 g metformin OUTCOMES: HbA1c, FPG, hypoglycaemia, safety, % reaching target HbA1c/FBG	appropriate and clearly focused question: adequately addressed in/exclusion criteria described: poorly addressed literature search sufficiently rigorous to identify all relevant studies: poorly addressed study selection described: not reported data extraction described: not reported study quality assessed and taken into account: not reported study flow shown: not reported study characteristics of individual studies described: adequately addressed quality of individual studies given: not reported results of individual studies shown: adequately addressed enough similarities

Review	Inclusion criteria and methodology	Included studies	Quality
			between studies selected to make combining them reasonable: not applicable how well was study done to minimise bias: (-) what is the likely direction in which bias might affect study results? less effect than reported
Horvath 2007 focus: effects of long-term treatment with long-acting insulin analogues (insulin glargine and insulin detemir) compared to NPH insulin in patients with type 2 diabetes mellitus funding: non-industrial	INCLUSION CRITERIA study design: randomised controlled trials with parallel or cross-over design, blinded or open-label, with a duration of 24 weeks or longer participants: patients with type 2 diabetes interventions: long-acting insulin analgues (glargine or detemir) versus NPH insulin; in case of combination with oral agents, the antihyperglycaemic agent had to be part of each treatment arm; subcutaneous applications for insulin only outcomes: primary: overall, severe and nocturnal hypoglycaemia; glycaemic control (HbA1c); secondary: mortality, cardiovascular morbidity, diabetic late complications, quality of life, adverse events, costs. METHODOLOGY search strategy: databases searched: Cochrane Library, Medline, Embase, CRD Databases; electronic search strategy shown; citation searches of included trials and reviews; additional internet searches listed; information	number of included trials: 7 RCTs insulin glargine versus NPH (6 analysed, see below), 2 RCTs insulin detemir versus NPH number of participants: (in analysed trials) 3151 for glargine trials (range 110 to 764), 980 for for detemir trials (505 and 475) TRIALS: design: all studies were parallel trials; 2 had a superiority design, 1 and equivalence and 2 a non-inferiority design; in none of the trials participants or caregivers were blinded duration: 6 to 12 months quality: all studies rated as being of insufficient methodological quality (rating C); reporting of randomisation poor in most trials, adequate allocation concealment in 5 trials; discontinuation rates 1.6 to 10.2%; all main analyses used ITT approach origin: 4 trials Europe, 2 North America, 1 Europe and South Africa, 1 Latin America funding: 5 trials were commercially funded, unclear for the rest	appropriate and clearly focused question: well covered in/exclusion criteria described: well covered literature search sufficiently rigorous to identify all relevant studies: well covered study selection described: well covered data extraction described: well covered study quality assessed and taken into account: well covered study flow shown: well covered study characteristics of individual studies

Review	Inclusion criteria and methodology	Included studies	Quality
	on unpublished trials sought from Sanofi-Aventis and Novo Nordisk. study selection: two reviewers independently screened titles and abstracts; full articles obtained for citations that appeared to fulfil the inclusion criteria (or in case of disagreement); if disagreement persisted, resolved by a third party. quality assessment: independent assessment of quality by two reviewers; differences in opinion resolved by discussion with a third reviewer; quality parameters assessed: randomisation, allocation concealment, blinding, description of withdrawals and drop-outs, ITT analysis, blinding of outcome assessors data extraction: done independently by two reviewers using data extraction sheets; differences in data extraction resolved by consensus; information extracted listed meta-analysis: yes data analysis: weighted mean differences or odds ratios calculated, random effects model used; heterogeneity assessed using chi-squared test subgroups / sensitivity analyses: planned but not carried out	PARTICIPANTS age: mean age 55 to 62 years gender: numbers given but partially unclear if they refer to men or women, distribution looks balanced BMI: mean 27 to 33 kg/m2 diabetes duration: mean 8 to 14 years HbA1c: mean 7.9 to 9.5% previous medication: no details, none of the trials was performed with pharmaco-naïve patients (i.e. controlled on diet/exercise only) INTERVENTIONS: 6 studies used combinations with oral anti-diabetic drugs (5 glargine and 1 detemir), 2 with a short-acting insulin (1 glargine and 1 detemir), and 1 with both (detemir); 1 study required an upward titration of insulin glargine with a target of a fraction of 50% of the basal insulin requirement while the fraction of NPH on the total insulin requirement was left unchanged, thus introducing a difference in the treatments, and the study was therefore not considered further; 1 study compared morning or evening glargine with evening NPH, in all other studies glargine or NPH were injected at bedtime (1 study choice of bedtime or twice daily); two studies (glargine) changed from previous oral antihyperglycaemic treatment to glimepiride during run-in OUTCOMES: glycaemic control (HbA1c), hypoglycaemia, FBG, blood glucose profiles, % reaching target HbA1c, insulin doses, weight change, adverse events	described: well covered quality of individual studies given: well covered results of individual studies shown: well covered enough similarities between studies selected to make combining them reasonable: well covered how well was study done to minimise bias: (++) what is the likely direction in which bias might affect study results? no likely bias
Tran 2007 focus: clinical and cost-	INCLUSION CRITERIA study design: randomised controlled trials participants: patients with diabetes mellitus	number of included trials: 9 RCTs insulin glargine, 2 RCTs insulin detemir (type 2 diabetes)	appropriate and clearly focused question: well covered in/exclusion criteria

Review	Inclusion criteria and methodology	Included studies	Quality
effectiveness of long-acting insulin analogues (insulin glargine and insulin detemir) for the treatment of diabetes melitus (both type 1 and 2) funding: Canadian Agency for Drugs and Technology in Health	(type 1, type 2 or gestational – only type 2 considered here) interventions: long-acting insulin analogues (insulin glargine or detemir) versus conventional human insulin or oral anti-diabetic agents outcomes: glycaemic control (blood glucose, HbA1c), quality of life, hypoglycaemic episodes, adverse events, complications of diabetes, mortality. METHODOLOGY search strategy: databases searched: Medline, BIOSIS Previews, Pascal, Embase, Pubmed, Cochrane Database of Systematic Reviews from 1990 onwards; electronic search strategy given; alert searches; grey literature obtained by searching listed web sites; manufacturers were asked to provide relevant information. study selection: two reviewers independently selected trials for inclusion; differences in decision resolved by consensus. quality assessment: Jadad scale; allocation concealment, blinding of assessors, intention-to-treat analysis. data extraction: one reviewer extracted data into a structured form, another reviewer checked the extraction. meta-analysis: yes data analysis: fixed and random effects models; heterogeneity assessed using Higgins' I2 value; weighted mean differences, relative risks and risk differences computed. subgroups / sensitivity analyses: none	number of participants: 4729 (range 110 to 756) TRIALS: design: all open-label parallel trials; 10 full publications, 2 abstracts/posters; most studies described as multi-centre duration: 4 to 52 weeks quality: for full reports, mean Jadad score 2.4 SD0.7, allocation concealment adequate in 4 studies (unclear in remainder), 90% reported ITT analysis origin: 4 trials Europe, 4 trials North America, 2 trials Europe and South Africa, 1 trial international funding: industrial (where reported) PARTICIPANTS age: mean 53 to 61 years (where reported) gender: 36 to 49% female (where reported) BMI: mean 27 to 35 kg/m2 diabetes duration: mean 8.5 to 13.8 years (where reported) HbA1c: mean 8.4 to 9.8% previous medication: see below INTERVENTIONS: 7 studies including various combinations of oral anti-hyperglycaemic medications, 1 study morning versus evening glargine versus evening NPH, 1 study combination with insulin aspart OUTCOMES: no specific details given, results reported for: glycaemic control, 8-point glucose profiles, hypoglycaemia, adverse events, mortality, quality of life	described: well covered literature search sufficiently rigorous to identify all relevant studies: well covered study selection described: well covered data extraction described: adequately addressed study quality assessed and taken into account: well covered study flow shown: well covered study characteristics of individual studies described: well covered quality of individual studies given: well covered results of individual studies shown: well covered enough similarities between studies selected to make combining them reasonable: yes how well was study done to minimise bias: (++) what is the likely

Review	Inclusion criteria and methodology	Included studies	Quality
			direction in which bias might affect study results? no likely bias
Warren 2004 focus: clinical and cost-effectiveness of insulin glargine in its licensed basal-bolus indication (both type 1 and type 2 diabetes) funding: NICE, UK	INCLUSION CRITERIA study design: methodology including at least one of: a) systematic review, b) RCT, c) economic evaluations; study duration at least 4 weeks participants: patients with type 1 or type 2 diabetes, requiring insulin for glycaemic control (only type 2 considered here) interventions: insulin glargine versus other long-acting basal insulin outcomes: glycaemic control (blood glucose, HbA1c); incidence and severity of hypoglycaemic episodes METHODOLOGY search strategy: databases searched: Biological Abstracts, CINAHL, Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, EBM Reviews, Embase, HTA Database, Medline, NHS Economic Evaluations Database, OHE Health Economic Evaluations Database, PreMedline, Science Citation Index, Social Sciences Citation Index; electronic search strategies given; searching of reference lists of relevant publications; 45 health services research related resources searched via the internet (list given); citation searches of key papers; no date, language, study or publication type restrictions; list provided by Aventis of peer-reviewed articles of glargine primary research. study selection: titles and abstracts screened; full copies of primary research reports, reviews	number of included trials: 5 RCTs for type 2 diabetes number of participants: 1399 (range 100 to 518) TRIALS: design: all prospective, 3 clearly described as RCTs, none double-blind, design not clearly documented for 2 trials; 2 full publications, 3 abstracts; most studies described as multi-centre duration: 4 to 52 weeks quality: assessment only possible for 2 articles reported in full; both scored 2 (of 3) on Jadad scale; blinding of patients not possible; none of the studies specified blinded outcome assessment origin: 1 trial Europe, 4 trials USA funding: not reported PARTICIPANTS: age: ~ 59 years (where reported) gender: 47 to 38% female (where reported) BMI: mean 29 to 31 kg/m2 (where reported) diabetes duration: 10 to 14 years (where reported) HbA1c: mean 8.5 to 9.1% (where reported) previous medication: see below, no details INTERVENTIONS: 2 studies of 2 formulations of insulin glargine compared to each other and to NPH, 3 studies of glargine compared to NPH; 2 studies of patients previously on insulin; 3 studies of patients previously on oral medication (and continuing oral medication); insulin doses individually titrated to achieve target FBG levels; titration periods of varying durations	appropriate and clearly focused question: well covered in/exclusion criteria described: well covered literature search sufficiently rigorous to identify all relevant studies: well covered study selection described: adequately addressed data extraction described: not adequately addressed study quality assessed and taken into account: well covered study flow shown: poorly addressed study characteristics of individual studies described: well covered quality of individual studies given: well covered results of individual studies shown: well covered enough similarities between studies selected to make

Review	Inclusion criteria and methodology	Included studies	Quality
	and abstracts obtained; no further details. quality assessment: Jadad scale; blinding of outcome assessment data extraction: done by one reviewer using customised data extraction sheets meta-analysis: no data analysis: text and tables subgroups / sensitivity analyses: none	OUTCOMES: glycaemic control, hypoglycaemia, FBG, diurnal blood glucose, % reaching target FBG	combining them reasonable: not applicable how well was study done to minimise bias: (+) what is the likely direction in which bias might affect study results? no likely bias
Wang 2003 focus: efficacy and tolerability of insulin glargine funding: not reported	INCLUSION CRITERIA study design: clinical trials, ≥100 participants; includes pharmacodynamic studies, only clinical efficacy trials considered here participants: type 1 or type 2 diabetes, only type 2 diabetes considered here interventions: insulin glargine (no details) outcomes: HbA1c, fasting plasma glucose (FPG), fasting blood glucose (FBG), incidence of hypoglycaemia, measures of tolerability METHODOLOGY search strategy: Medline / Pubmed, Embase (1966 to 2002), Premedline (Nov 2002); search words given; searching of reference lists of relevant publications study selection: not described quality assessment: not described data extraction: not described meta-analysis: no data analysis: not described subgroups / sensitivity analyses: none	number of included trials: 7 RCTs for efficacy, 1 RCT for quality of life number of participants: 2856 (range 100 to 756) TRIALS: design: all trials multi-centre, open-label, randomised trials duration: 4 to 52 weeks quality: inconsistent reporting of mean or adjusted mean changes in primary and secondary efficacy endpoints within and between treatment groups; studies were typically statistically underpowered (only 3 studies included power analysis); 5 studies only available in abstract form origin: Europe and USA funding: unclear, some industrial, indicated that for most studies authors may have had conflicts of interest PARTICIPANTS: age: ~ 59 years gender: not reported BMI: only reported for 2 studies, mean 29 to 32 kg/m2 diabetes duration: not reported HbA1c: mean 8.4 to 9.0% (where reported)	appropriate and clearly focused question: adequately addressed in/exclusion criteria described: poorly addressed literature search sufficiently rigorous to identify all relevant studies: adequately addressed study selection described: not reported data extraction described: not reported study quality assessed and taken into account: poorly addressed study flow shown: not reported study characteristics of individual studies described: adequately

Review	Inclusion criteria and methodology	Included studies	Quality
		previous medication: see below, no details INTERVENTIONS: insulin doses individually titrated to achieve target FBG level of ≤120 mg/dL (6.7 mmol/L) (≤100 mg/dL in Fritsche 2002 and Riddle 2002); 2 trials comparing 2 formulations of insulin glargine (containing 30 or 80 µg/mL of zinc); 3 trials of patients not receiving oral anti-diabetic drugs with previous once or twice daily NPH insulin with or without short-acting insulin for post-prandial control; 4 studies comparing once daily insulin glargine with once daily NPH insulin in previously insulin-naïve patients also taking oral anti-diabetic agents OUTCOMES: HbA1c, FPG, self-monitored FBG levels, incidence of hypoglycaemia	addressed quality of individual studies given: poorly addressed results of individual studies shown: adequately addressed enough similarities between studies selected to make combining them reasonable: not applicable how well was study done to minimise bias: (-) what is the likely direction in which bias might affect study results? less effect than reported

Results by review

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
all studies – glargine versus NPH insulin				
HbA1c				
Horvath 2007	HbA1c (%) (studies with available data)	4	weighted mean difference 0.1% (95% CI: -0.1, 0.2)	p=NS
	HbA1c (%) (all studies, pooled SD)	6	weighted mean difference 0.00% (95% CI: -0.1, 0.1)	p=NS

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
Tran 2007	HbA1c (%)	7	meta-analysis weighted mean difference 0.05 (95% CI: -0.07, 0.16)	p=NS; no significant difference for analysis by different co-interventions
hypoglycaemia				
Horvath 2007	severe hypoglycaemia	4	meta-analysis, 6-month studies only Peto odds ratio 0.70 (95% CI: 0.40, 1.23)	p=NS; no significant difference or no statistical information for remaining 3 studies
	symptomatic hypoglycaemia	3	meta-analysis, 6-month studies only relative risk 0.84 (95% CI: 0.75, 0.95)	significantly fewer with glargine, p=0.005; for remaining 4 studies: 3 studies no significant difference, 1 significant in favour of glargine (p<0.02)
	overall hypoglycaemia	1	morning glargine: 74% evening glargine: 68% evening NPH insulin: 75%	p=NS
	nocturnal hypoglycaemia	3	meta-analysis, 6-month studies only relative risk 0.66 (95% CI: 0.55, 0.80)	significantly fewer with glargine, p<0.0001; also significant results for the 3 studies not included in the meta-analysis but reporting on nocturnal hypoglycaemia
Tran 2007	overall hypoglycaemia	6	meta-analysis relative risk 0.89 (95% CI : 0.83, 0.96), NNT 14 (95% CI : 9, 33)	p=0.002; no significant difference for analysis by different co-interventions
	severe hypoglycaemia	4	meta-analysis relative risk 1.09 (95% CI : 0.56, 2.12)	p=NS; no significant difference for analysis by different co-interventions
	nocturnal hypoglycaemia	5	meta-analysis relative risk 0.57 (95% CI : 0.44, 0.74), NNT 8 (95% CI : 6, 11)	p<0.0001; no significant difference for analysis by different co-interventions
glycaemic excursions				
Tran 2007	8-point blood glucose profiles	3		generally no statistically significant difference between glucose profiles for glargine versus NPH; pre-dinner values lower in two studies for

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
				glargine, and in one study for morning (but not evening) glargine versus evening NPH
total daily dose	not reported			
weight change	not reported			
complication rates				
Horvath 2007	mortality	3	small numbers, no study adequately powered to assess this parameter	
	new development of non-proliferative retinopathy	1	glargine: 8.4% NPH insulin: 14%	p-value not reported
	development of clinically significant macular oedema (of people with no retinopathy)	1	glargine: 1.8% NPH insulin: 2.4%	p-value not reported
	progression of retinopathy by more than 3 stages	2	glargine: 5.9 to 7.5% NPH insulin: 2.7 to 9.1%	p-value not reported for one study, significantly more with glargine in the other study p=0.028
	development of clinically significant macular oedema	1	glargine: 11.2% NPH insulin: 6.5%	p=NS
Tran 2007	mortality	4		none of reported deaths thought to be related to study medication
adverse events				
Horvath 2007	overall adverse events	4		numbers comparable between groups
	serious adverse events	2		numbers comparable between groups
	adverse events possibly related to treatment	4		numbers comparable between groups
	patients withdrawing due to adverse events	6		numbers comparable between groups
Tran 2007	adverse events	10		no significant differences in adverse

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
				events between glargine and NPH
HR quality of life				
Horvath 2007	Diabetes Treatment and Satisfaction Questionnaire	1	more pronounced improvement of treatment satisfaction reported with glargine versus NPH	p<0.05
previous insulin – glargine versus NPH insulin				
HbA1c				
Duckworth 2007	HbA1c (%)	2	glargine: -0.41% NPH insulin: -0.46% to -0.59%	change in HbA1c similar between groups
	target reached (HbA1c ≤7.0 to ≤7.5; FBG ≤6.7 mmol/L)	2	HbA1c glargine: 18% NPH insulin: 18% FBG glargine: 29.6 to 34% NPH insulin: 24 to 27.1%	similar between groups for both studies
Wang 2003	HbA1c (%)	2	glargine: -0.35% to -0.41% NPH insulin: -0.44% to -0.59%	p=NS in one study, not reported for the other
Warren 2004	HbA1c (%)	2	glargine: -0.35% NPH insulin: -0.44% numbers only reported for one	p=NS for both
	patients reaching target FBG	1	glargine: 29.6% NPH insulin: 27.1%	p=NS
hypoglycaemia				
Duckworth 2007	overall symptomatic hypoglycaemia	2	glargine: 46 to 61.4 % NPH insulin: 60 to 66.8 %	p<0.05 in one study, p=NS in the other
	severe hypoglycaemia	2	glargine: 0 to 0.4% NPH insulin: 2.0 to 2.3%	p=NS
	nocturnal hypoglycaemia	2	glargine: 15 to 26.5% NPH insulin: 27 to 35.5%	p<0.05 in one study, p=NS in the other
Wang 2003	≥1 episode of	1	glargine: 46.2%	p=0.048

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
	hypoglycaemia		NPH insulin: 60.4%	
	reported nocturnal hypoglycaemic events	2	glargine: 15.4% to 31.3% NPH insulin: 27.1% to 40.2%	p=NS in one study, p=0.014 in other study
	symptomatic hypoglycaemia	2	glargine: 17.3% to 61.4% NPH insulin: 31.3% to 66.8%	p=NS in 1 study, p=0.002 in the other
	episodes of severe hypoglycaemia	1	glargine: 6.6% (-0.4%) NPH insulin: 10.4% (-2.3%)	p=NS
Warren 2004	symptomatic hypoglycaemia	2	glargine: 6.6 to 17.3% NPH insulin: 10.4 to 31.3%	p=NS in one study, p<0.05 in the other study
	nocturnal hypoglycaemia	2	glargine: 15.4 to 35% NPH insulin: 27.1 to 43.7%	p=NS in one study, p<0.05 in the other study
	severe hypoglycaemia	2	not reported separately	
glycaemic excursions	not reported			
total daily dose				
Warren 2004	insulin use	1	for patients on pre-trial once-daily NPH, slightly more insulin used at trial end than at baseline (no data presented) for patients on pre-trial more than once-daily NPH, people on glargine used slightly less at trial end (reduced by 4.4 U/day) and patients treated with NPH used about the same (no more data presented)	unclear
weight change				
Wang 2003	weight gain	1	glargine: +0.4 kg NPH insulin: +1.4 kg p<0.001, CIs not reported	
complication rates				
adverse events				
Wang 2003	injection site pain	1	28 weeks greater number of patients reported injection site pain with insulin glargine compared with	

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
			NPH insulin (pain usually mild and did not result in discontinuation of treatment)	
Warren 2004	injection site pain	1	glargine: 10.4% NPH insulin: 7.7%	unclear, probably p<0.05; but mild and no drop-outs as a result
	insulin antibodies	1	no increases in either comparison group	
HR QoL	not reported			
insulin-naïve, oral antihyperglycaemics – glargine versus NPH insulin				
HbA1c				
Duckworth 2007	HbA1c (%)	5	glargine: -0.46 to -2.36% NPH insulin: -0.38 to -2.44%	4 trials HbA1c similar between groups, 1 trial significantly more HbA1c reduction with morning glargine than bedtime NPH (p<0.001) and with morning glargine versus bedtime glargine (p=0.009)
	target reached (HbA1c ≤7.0 to ≤7.5; FBG ≤6.7 mmol/L)	4	HbA1c glargine: 33 to 58% NPH insulin: 32 to 57.3% FBG glargine: 40.7 to 42% NPH insulin: 35.1 to 44%	3 trials no significant difference, 1 trial significantly more patients reaching target with morning glargine than with bedtime glargine or NPH (p<0.05)
Wang 2003	HbA1c (%)	4	glargine: -0.76% to -1.64% NPH insulin: -0.66 to -1.63%	3 trials no significant difference between glargine and NPH, 1 trial significantly more HbA1c reduction with morning glargine than bedtime NPH (p<0.001) and with morning glargine versus bedtime glargine (p=0.009)
	target reached (≤7.0% to <8.0%)	2	glargine: 53.8 to 57.9% NPH insulin: 43.9 to 57%	1 study p=NS, 1 study unclear
Warren 2004	HbA1c (%)	3	glargine: -0.8%	p=NS for all studies

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
			NPH insulin: -0.8% numbers only reported for one	
	patients reaching target FBG	1	glargine: 7.7% NPH insulin: 7.6%	p=NS
hypoglycaemia				
Duckworth 2007	overall symptomatic hypoglycaemia	6	glargine: 18.8 to 56%, 5.5 to 13.9 events/patient-year NPH insulin: 32.4 to 58%, 8.0 to 17.7 events/patient-year	p<0.05 in 4 studies, p=NS in 2 studies
	severe hypoglycaemia	2	glargine: 0 to 2.5% NPH insulin: 0 to 1.8%	p=NS
	nocturnal hypoglycaemia	5	glargine: 7.3 to 23%, 4.0 events/patient-year NPH insulin: 19.1 to 38%, 6.9 events/patient-year	p<0.05 in all studies
Wang 2003	hypoglycaemic episodes (%)	2	glargine: 7.3% to 33% NPH insulin: 19.1% to 43%	p<0.05 for both studies
	nocturnal hypoglycaemia	3	glargine: 9.9 to 47% NPH insulin: 24 to 55%	p<0.05 for all studies
	achieving HbA1c ≤7.0%without nocturnal hypoglycaemia	1	glargine: 33% NPH insulin: 27%	p<0.05
	severe Hypoglycaemia	1	glargine: 2.5% NPH insulin: 2.3%	p=NS
Warren 2004	symptomatic hypoglycaemia	2	glargine: 7.3% NPH insulin: 19.1% numbers only for one trial	p<0.05 for both
	nocturnal hypoglycaemia	1	no numbers reported in trial	significantly fewer in glargine group, p=0.0001
	severe hypoglycaemia	0	not reported by studies	
glycaemic excursions				
Wang 2003		1	change in FPG levels significantly greater	

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
			both before and after dinner with insulin glargine (p=0.035, no details); FPG levels at 3:00 am similar between groups (glargine: 133 SE3.6 mg/dL; NPH: 131.4 SE3.6 mg/dL)	
total daily dose				
Warren 2004	insulin use	1	glargine: 23 U/day NPH insulin: 21 U/day	unclear
weight change				
Wang 2003		2	glargine: no change to +2.57 kg NPH insulin: no change to +2.34 kg	p=NS for both studies
complication rates	not reported			
adverse events				
Wang 2003	injection site pain	1	greater number of patients reported injection site pain with insulin glargine compared with NPH insulin (pain usually mild and did not result in discontinuation of treatment)	
Warren 2004	insulin antibodies	1	no increases in either comparison group	
HR quality of life				
Wang 2003	Diabetes Treatment Satisfaction Well-Being Questionnaire	1	no numeric data reported; increases in treatment satisfaction significantly greater for insulin glargine compared to NPH insulin at week 36 (p=0.033); small increase in the perceived frequency of hypoglycaemia in both groups, but no significant difference between groups	
fasting plasma glucose (where HbA1c not reported)				
Duckworth 2007	FPG	1	not reported for groups separately, decrease from baseline -3.10 to -3.49 mmol/L	similar between groups
Wang 2003	FPG	1	glargine with 30 µg/mL zinc: -2.8 mmol/L glargine with 80 µg/mL zinc: -2.6 mmol/L	p-value not reported

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
			NPH insulin: -2.3 mmol/L	
all studies – detemir versus NPH insulin				
HbA1c				
Horvath 2007	HbA1c (%)	2	meta-analysis using different ways of estimating missing SDs weighted mean difference 0.12% (95% CI: 0.01, 0.23) weighted mean difference with pooled SD 0.15% (95% CI: -0.02, 0.32)	first calculation yields significant result (p=0.03) in favour of NPH, but well within pre-defined non-inferiority margin of 0.4% HbA1c; second calculation p=NS
Tran 2007	HbA1c (%)	2	meta-analysis weighted mean difference 0.11% (95% CI: -0.03, 0.26)	p=NS; no significant difference for analysis by different co-interventions
hypoglycaemia				
Horvath 2007	severe hypoglycaemia	2	meta-analysis Peto odds ratio 0.5 (95% CI: 0.18, 1.38)	p=NS
	symptomatic hypoglycaemia	1	detemir: 4.9 events/patient/year NPH insulin: 9.7 events/patient/year relative risk 0.56 (95% CI: 0.42, 0.74)	p<0.001
	overall hypoglycaemia	2	meta-analysis relative risk 0.82 (95% CI: 0.74, 0.90)	p<0.0001
	nocturnal hypoglycaemia	2	meta-analysis relative risk 0.63 (95% CI: 0.52, 0.76)	p<0.00001
Tran 2007	overall hypoglycaemia	1	relative risk 0.91 (95% CI: 0.75, 1.11)	p=NS
	nocturnal hypoglycaemia	1	relative risk 0.66 (95% CI: 0.45, 0.96)	p<0.05
glycaemic excursions				
Tran 2007	8-point blood glucose profiles	2		glucose profiles similar for detemir versus NPH; no difference depending on co-intervention (insulin aspart or oral anti-hyperglycaemic agents)
total daily dose	not reported			

Study	Outcome (specific time point?)	n (studies)	Results – magnitude of change / difference	Statistical significance
weight change				
Horvath 2007	weight change	2	difference in weight gain between detemir and NPH -0.8 to -1.6 kg	p<0.05
complication rates				
Horvath 2007	mortality	1	small numbers, no study adequately powered to assess this parameter	
	cardiovascular morbidity	1	very small numbers, no conclusions can be drawn	
	diabetic late complications	1	very small numbers, no conclusions can be drawn	
Tran 2007	mortality	1		none of reported deaths thought to be related to study medication
adverse events				
Horvath 2007	adverse events	2	no difference in frequency of adverse events	
Tran 2007	adverse events	1		no significant differences in adverse events between detemir and NPH
HR quality of life	not reported			

Description of studies

Study	Design	Participants	Interventions	Outcome measures
insulin-naïve, oral antihyperglycaemics – glargine versus NPH insulin				(indicate method of assessment)
Pan 2007 (LEAD study) China, France, Korea	focus: effect of insulin glargine versus NPH insulin on metabolic control and safety in Asian patients with type 2 diabetes, inadequately controlled on oral	total number: 443 N glargine: 220; 198 completed the trial N NPH: 223; 201 completed the trial inclusion criteria: insulin-naïve; Asian; aged ≥40 and ≤80 years; type 2	glargine: insulin glargine once daily at bedtime (21-23 h), once daily glimepiride (3 mg) in the morning (7-9 h) NPH: NPH insulin once daily at bedtime (21-23 h), once daily glimepiride (3 mg) in	primary: change in HbA1c level from baseline to endpoint HbA1c: HbA1c, proportion of patients with HbA1c <7.5%, proportion of combined responders (both

Study	Design	Participants	Interventions	Outcome measures
	antihyperglyceamic agents design: non-inferiority study; open-label, parallel group randomised trial multi-centre duration: 24 weeks follow-up: no post-intervention follow-up setting: funding: Sanofi-Aventis Korea	diabetes according to WHO criteria plus specified blood glucose criteria; poorly controlled on oral hypoglycaemic agents for ≥3 months before study entry; BMI 20-35 kg/m2; HbA1c ≥7.5 and ≤10.5%, fasting blood glucose levels >120 mg/dL (>6.7 mmol/L) exclusion criteria: pregnancy; history of ketoacidosis; likelihood of requiring treatment with drugs prohibited by the protocol (e.g. non-selective beta-blockers, systemic corticosteroids) age: glargine: 55.6 SD8.4 years; NPH: 56.6 SD8.7 years gender: glargine: 59.6% female; NPH: 55.6% female BMI: glargine: 24.8 SD3.1 kg/m2; NPH: 25.1 SD3.3 kg/m2 ethnicity: n=126 China, 26 Hong Kong, 19 Indonesia, 112 South Korea, 16 Malaysia, 36 Pakistan, 24 Philippines, 32 Taiwan, 48 Thailand, 4 Singapore diabetes duration: glargine: 10.3 SD6.3 years; NPH: 10.0 SD5.4 years previous medication: not reported, duration of treatment with oral antihyperglycaemic agents: glargine: 9.1 SD6.0 years; NPH: 8.6 SD5.2 years comorbidities: not reported subgroups: none	the morning (7-9 h) both: insulin glargine / NPH insulin titrated to a target FBG ≤120 mg/dL (≤6.7 mmol/L), starting at insulin dose of 0.15 U/kg/day co-interventions: none adherence assessment: no screening phase: 3-4 weeks, oral treatments standardised to 3 mg glimepiride, patients were given training in self-administration of insulin and self-monitoring of blood glucose levels	HbA1c <7.5% and FBG levels ≤120 mg/dL) hypoglycaemia: proportion of patients with hypoglycaemia; severe hypoglycaemia (symptoms consistent with hypoglycaemia, BG <50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose or glucagons administration and the requirement of third party assistance); nocturnal hypoglycaemia (while patient was asleep) glycaemic excursions: yes, blood glucose profiles total daily dose: yes weight change: BMI complication rates: no adverse events: yes health-related quality of life: no other: none timing of assessment: baseline, 2, 4, 6, 8, 12, 16, 20 and 24 weeks after randomisation
previous insulin – detemir versus NPH insulin				

Study	Design	Participants	Interventions	Outcome measures
Montanana 2007 (PREDICTIVE-BMI trial) Spain abstract only	focus: weight change caused by detemir or NPH used as part of basal-bolus regimen in already overweight type 2 diabetes patients design: parallel group randomised controlled trial multi-centre duration: 26 weeks follow-up: no post-intervention follow-up setting: unclear funding: Novo Nordisk	total number: 271 N detemir: 125 N NPH: 146 inclusion criteria: men or women ≥18 years, type 2 diabetes, had been receiving 2 daily doses (at least one premix) for ≥3 months; HbA1c between 7.5 and 11%; BMI between 25 and 40 kg/m2 exclusion criteria: not reported age: not reported gender: not reported BMI / weight: detemir: 31.6 kg/m2 / 79.5 kg; C: 32.2kg/m2 / 82.2 kg ethnicity: not reported diabetes duration: not reported previous medication: not reported comorbidities: not reported subgroups: none	detemir: once daily (evening) detemir NPH: once daily (evening) NPH both: basal insulin continually and individually titrated, aiming for pre-breakfast plasma glucose of ≤6.1 mmol/L without levels of hypoglycaemia considered unacceptable to the patient co-interventions: all patients received insulin aspart at main meals (individually titrated aiming for postprandial glucose levels of ≤10.0 mmol/L); concomitant treatment with metformin also allowed (used by ~50% of patients on detemir and ~58% of patients on NPH) adherence assessment: not reported	primary: unclear (weight change?) HbA1c: yes hypoglycaemia: yes; all, severe, nocturnal hypoglycaemic events glycaemic excursions: no total daily dose: no weight change: yes complication rates: no adverse events: no health-related quality of life: no other: none timing of assessment: not reported
insulin-naïve – detemir versus NPH insulin				
Philis-Tsimikas 2006 Denmark, France, Italy, The Netherlands, Norway, Spain, USA	focus: effectiveness and tolerability of detemir versus NPH once daily with one or more oral anti-diabetic in people with poorly controlled type 2 diabetes design: multi-centre, randomised, open-label, 3-arm parallel trial	total number: 504 enrolled, 498 in ITT analysis N morning detemir: 165, 149 completed the trial N evening detemir: 169, 154 completed the trial N evening NPH: 164, 149 completed the trial inclusion criteria: age ≥18 years, BMI	N morning detemir: insulin detemir once daily before breakfast N evening detemir: insulin detemir once daily in the evening (=interval 1 hour before last meal until bedtime) N evening NPH: human NPH insulin once daily in the	primary: HbA1c HbA1c: yes hypoglycaemia: yes; major episodes (requiring third party assistance), confirmed episodes (plasma glucose reading <3.1 mmol/L, patients able to self-manage the event), nocturnal hypoglycaemia (between

Study	Design	Participants	Interventions	Outcome measures
	multi-centre duration: 20 weeks follow-up: no post-intervention follow-up setting: outpatient clinic funding: Novo Nordisk	≤40 kg/m2, diagnosis of type 2 diabetes since at least 12 months, insulin-naïve, HbA1c between 7.5 and 11% after at least 3 months' treatment with one or more oral anti-diabetic agent (OAD); OAD therapy was therapy with metformin or an insulin secretagogue or a combination of the two, at least half the recommended maximum dose; at US centres, concomitant treatment with thiazolidinedione (TZD) was permitted throughout study period, at European centres TZD was to be discontinued before initiation of insulin treatment; use of alpha-glucosidase inhibitor was permitted but only in combination with another OAD exclusion criteria: proliferative retinopathy/maculopathy requiring treatment, hypoglycaemia unawareness or recurrent major hypoglycaemia, use or anticipated use of ≥1 drug likely to affect blood glucose regulation (e.g. systemic steroids, nonselective beta-blockers, monoamine oxidase inhibitors), OAD treatment not adhering to approved labelling in the respective country; any disease or condition that would make patient unsuitable for participation (e.g. renal, hepatic, cardiac disease), uncontrolled hypertension, any psychological incapacity or language barrier precluding adequate understanding or cooperation	evening all groups: insulin injected via pen device, participants advised to keep time of injection constant and to inject insulin subcutaneously, preferably in the thigh, but to rotate sites; initial dose of treatment was 10 IU (U), doses were titrated at clinic visits or by telephone at least once every 4 weeks based on the mean of 3 plasma glucose levels measured on 3 consecutive days; in patients receiving detemir in the morning, the dose was titrated to aim for pre-dinner plasma glucose concentration of ≤6.0 mmol/L; in patients receiving detemir or NPH in the evening, titration was aimed to achieve pre-breakfast plasma glucose concentration of ≤6.0 mmol/L co-interventions: OAD therapy and dose was to remain unchanged; other co-interventions (similar between groups): ~21% used acetylsalicylic acid, ~19% simvastatin, ~15% atorvastatin adherence assessment: not reported	11 pm and 6 am) glycaemic excursions: 9-point self-measured plasma glucose profiles (using capillary blood and plasma-calibrated monitor): immediately before and 90 min after main meals, bedtime, 3 am; additional measurements when patients experienced symptoms indicative of hypoglycaemia total daily dose: yes weight change: yes (calibrated scales) complication rates: no adverse events: adverse events, standard laboratory analyses, fundoscopy, physical examination health-related quality of life: no other: none timing of assessment: at least 9 telephone contacts and 6 clinic visits (including screening and randomisation)

Study	Design	Participants	Interventions	Outcome measures
		age: morning detemir: 58.3 SD10.4 years; evening detemir: 58.7 SD10.2 years; NPH insulin: 58.4 SD11.0 years gender: morning detemir: 40.6% female; evening detemir: 46.2% female; NPH insulin: 42.7% female BMI / weight: morning detemir: 29.8 SD5.0 kg/m2; evening detemir: 29.7 SD5.1 kg/m2; NPH insulin: 30.4 SD4.8 kg/m2 ethnicity: not reported diabetes duration: morning detemir: 10.5 SD7.6 years; evening detemir: 10.5 SD7.0 years; NPH insulin: 10.0 SD6.9 years previous medication: morning detemir: 26.1% OAD monotherapy (9.7% metformin, 16.4% secretagogue), 73.9% combination therapy (56.4% metformin + 1 or 2 secretagogues, 5.5% metformin + secretagogue + TZD, 6.7% 2 secretagogues, 1.8% secretagogue + TZD); evening detemir: 21.3% OAD monotherapy (8.3% metformin, 13.0% secretagogue), 78.7% combination therapy (53.8% metformin + 1 or 2 secretagogues, 8.9% metformin + secretagogue + TZD, 7.7% 2 secretagogues, 1.2% secretagogue + TZD); NPH insulin: 24.4% OAD monotherapy (9.8% metformin, 14.6% secretagogue), 75.6% combination therapy (53.0 % metformin + 1 or 2 secretagogues, 6.1% metformin + secretagogue + TZD, 9.1% 2 secretagogues, 1.2%		

Study	Design	Participants	Interventions	Outcome measures
		secretagogue + TZD) comorbidities: ~56% hypertension, ~29% hypercholesterolaemia, ~12% dyslipidaemia, ~11% diabetic retinopathy; similar occurrence in treatment groups subgroups: none		

Quality assessment of trials

	Pan 2007	Montanana 2007	Philis-Tsimikas 2006
appropriate and clearly focused question	yes	Yes	yes
method of randomisation	not described	not described	described, adequate
allocation concealed	not reported	not reported	unclear
participants blinded	no	not reported	no
outcome assessors blinded	no	not reported	no
all relevant outcomes measured in standard, valid, reliable way	yes	not reported	yes
proportion of participants excluded / lost to follow-up	4 patients withdrew consent after randomisation and received no study medication; 1 received medication but provided no outcome measures; 49 were excluded for major protocol violations; no further details	not reported	18, 16 and 17 in morning detemir, evening detemir and evening NPH groups, reasons listed, no significant difference between groups
handling of missing data	not reported	not reported	last observation carried forward
intention-to-treat analysis performed	yes	not reported	yes
statistical analysis appropriate	yes	not reported	yes, non-inferiority analysis
only difference between groups is treatment under investigation	yes	Yes	yes
results in multi-centre studies comparable for all sites	not reported	not reported	not reported
groups comparable at baseline	yes	Yes	yes

	Pan 2007	Montanana 2007	Philis-Tsimikas 2006
SUMMARY			
How well was study done to minimise bias: (++ / + / -)	(-)	unclear, abstract only	(+)
What is the likely direction in which bias might affect study results?	positive effects of study drug exaggerated		
Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	probably		yes
Are the results of this study directly applicable to the patient group targeted by this guideline?	no (Asian patients only)		yes

Results by study

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
insulin-naïve, oral antihyperglycaemics – glargine versus NPH insulin					
HbA1c					
Pan 2007 (LEAD study)	HbA1c (%)	glargine: 9.02 SD0.88 % NPH insulin: 9.05 SD0.84 %	glargine: 8.03% NPH insulin: 8.28%	glargine: -0.99% NPH insulin: -0.77% difference in ITT population 0.22 (95% CI: 0.02, 0.42)	p=NS for per-protocol population, p=0.0319 for ITT population
	patients achieving target HbA1c (<7.5%) (%)		glargine: 38.1% NPH insulin: 30.3%		p=NS
	patients achieving target HbA1c (<7.5%)		glargine: 22.9%		p=0.017

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
	without nocturnal hypoglycaemia (%)		NPH insulin: 14.0%		
	patients achieving target FBG (≤120 mg/dL) (%)		glargine: 62.3% NPH insulin: 58.7%		p=NS
hypoglycaemia					
Pan 2007 (LEAD study)	number of hypoglycaemic episodes		glargine: 682 NPH insulin: 1019		p<0.004
	symptomatic hypoglycaemia		glargine: 515 NPH insulin: 908		p<0.0003
	severe hypoglycaemia		glargine: 5 NPH insulin: 28		p<0.03
	nocturnal hypoglycaemic episodes		glargine: 221 NPH insulin: 620		p<0.001
glycaemic excursions					
Pan 2007 (LEAD study)	eight-point blood glucose profiles			eight-point blood glucose profiles similar between groups at study end, except for post-dinner, where BG concentration in glargine group was significantly lower than in NPH group (236 mg/dL versus 249 mg/dL, p=0.044)	
total daily dose					
Pan 2007 (LEAD study)	daily insulin dose	glargine: 9.6 SD1.5 U NPH insulin: 9.8 SD1.9 U	glargine: 32.1 SD17.6 U NPH insulin: 32.8 SD18.9 U		p=NS
weight change					

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
Pan 2007 (LEAD study)	BMI	glargine: 24.8 SD3.1 kg/m2 NPH insulin: 25.1 SD3.3 kg/m2		glargine: +1.40 kg/m2 NPH insulin: +1.29 kg/m2	p=NS
complication rates	not reported				
adverse events					
Pan 2007 (LEAD study)	treatment-emergent adverse events that were possibly treatment-related (66 events in 45 patients)		glargine: 22 patients NPH insulin: 23 patients majority related to injection-site reactions (45 events in 31 patients)		p not reported
	serious adverse events			no significant difference between groups, none of events considered unusual for the demographic group studied	p=NS
HR QoL	not reported				
previous insulin – detemir versus NPH insulin					
HbA1c					
Montanana 2007 (PREDICTIVE-BMI)	HbA1c	detemir: 8.9% NPH: 8.8%	detemir: 7.8% NPH: 7.8%		p=NS
hypoglycaemia					
Montanana 2007 (PREDICTIVE-BMI)	all hypoglycaemic events	not reported	not reported	significantly less in detemir group, relative risk 0.62	p<0.0001
	nocturnal hypoglycaemia	not reported	not reported	significantly less in detemir group, relative risk 0.43	p<0.0001
glycaemic excursions	not reported				
total daily dose	not reported				

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
weight change					
Montanana 2007 (PREDICTIVE-BMI)	weight change	detemir: 79.5 kg NPH: 82.2 kg	26 weeks detemir: +0.4 kg NPH: +1.9 kg	difference 1.5 kg	p<0.0001
	BMI	detemir: 31.6 kg/m2 NPH: 32.2 kg/m2	26 weeks detemir: +0.17 kg/m2 NPH: +0.77 kg/m2	difference 0.6 kg/m2	p<0.0001
complication rates	not reported				
adverse events	not reported				
HR QoL	not reported				
insulin-naïve, oral antihyperglycaemics – detemir versus NPH insulin					
HbA1c					
Philis-Tsimikas 2006	HbA1c (%)	morning detemir: 9.08 SD0.97 % evening detemir: 8.88 SD0.95 % NPH insulin: 9.15 SD1.0 %	morning detemir: 7.50 SD0.96 % evening detemir: 7.40 SD0.77 % NPH insulin: 7.35 SD0.93 %	morning detemir: -1.58 SD1.07 % evening detemir: -1.48 SD1.01 % NPH insulin: -1.74 SD1.08 %	p=NS
hypoglycaemia					
Philis-Tsimikas 2006	major episodes		morning detemir: 0 evening detemir: 2 events in 2 (1.2%) patients		too few events for statistical analysis

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
			NPH insulin: 0		
	all confirmed episodes		morning detemir: 91 events in 32 (19.4%) patients evening detemir: 82 events in 27 (16.0%) patients NPH insulin: 153 events in 53 (32.3%) patients	RR morning versus evening detemir: 1.43 morning detemir versus evening NPH: 0.68 evening detemir versus evening NPH: 0.47	morning detemir versus evening detemir or NPH p=NS; evening detemir versus evening NPH p=0.019
	nocturnal episodes		morning detemir: 6 events in 4 (2.4%) patients evening detemir: 19 events in 8 (4.7%) patients NPH insulin: 47 events in 22 (13.4%) patients (no major episodes occurred)	RR morning versus evening detemir: 0.35 morning detemir versus evening NPH: 0.13 evening detemir versus evening NPH: 0.35	morning detemir versus evening detemir p=NS; morning detemir versus evening NPH p<0.001; evening detemir versus evening NPH p=0.031
glycaemic excursions					
Philis-Tsimikas 2006	pre-breakfast self-measured plasma glucose (mmol/L)		morning detemir: 7.97 SD1.23 mmol/L evening		p<0.001 morning detemir versus evening detemir and evening NPH

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
			detemir: 6.50 SD1.28 mmol/L NPH insulin: 6.78 SD1.26 mmol/L		
	pre-dinner self-measured plasma glucose (mmol/L)		morning detemir: 7.11 SD1.91 mmol/L evening detemir: 7.76 SD1.84 mmol/L NPH insulin: 7.95 SD1.98 mmol/L		p=0.005 morning detemir versus evening detemir; p<0.001 morning detemir versus evening NPH
	9-point self-measured plasma glucose profile				similar for 2 evening insulin groups, mean profile of morning insulin detemir group was characterised by lower glycaemic values in the daytime and higher values overnight (p<0.001)
total daily dose					
Philis-Tsimikas 2006	mean insulin dose		morning detemir: 0.5 SD0.3 U/kg evening detemir: 0.4 SD0.2 U/kg NPH insulin: 0.4 SD0.2 U/kg		p=NS
weight change					
Philis-Tsimikas 2006	weight gain		morning detemir: +1.2 kg evening		morning detemir versus evening detemir or NPH p=NS; evening detemir versus evening NPH

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
			detemir: +0.7 kg NPH insulin: +1.6 kg		p=0.005
complication rates	not reported				
adverse events					
Philis-Tsimikas 2006	withdrawals due to adverse events		morning detemir: 2.4% evening detemir: 2.4% NPH insulin: 2.4%		
	overall profiles of adverse events		morning detemir: 123 AEs in 70 patients evening detemir: 150 AEs in 67 patients NPH insulin: 144 AEs in 82 patients		statistically similar, mostly considered unrelated to study insulins; all serious adverse events unrelated to insulins
	injection site reactions		morning detemir: 2 events in 2 patients evening detemir: 7 events in 6 patients NPH insulin: 2 events in 2 patients		p=NS

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
	potential allergic reactions		morning detemir: 2 events in 2 patients evening detemir: 5 events in 5 patients NPH insulin: 1 event in 1 patient		p=NS
HR QoL	not reported				

1.6 Included studies for the insulin and pioglitazone evidence review

Description of studies

Study	Design	Participants	Interventions	Outcome measures
Asnani 2006 USA	focus: effect of pioglitazone on vascular reactivity in patients with insulin-treated type 2 diabetes design: randomised, double-blind, placebo-controlled trial single centre duration: 4 months follow-up: no post-intervention follow-up funding: Takeda, NIH Risk of bias: ++	total number: 20 N PIO + ins: 10; 8 completed the trial N P + ins: 10; 8 completed the trial inclusion criteria: age 18-75, insulin-treated type 2 diabetes (with or without oral antidiabetic agents), poor glycaemic control (HbA1c >7.5%) exclusion criteria: active liver disease, pregnant or breast-feeding women, history or recent myocardial infarction within last 6 months, recent major surgery within last 6 months age: PIO + ins: 59 SD6 years; P + ins: 57 SD5 years gender: not reported	PIO + ins: pioglitazone 30 mg at breakfast, insulin continued as before P + ins: placebo, insulin continued as before co-interventions: stable lipid-lowering (statins) and antihypertensive therapy (including ACE inhibitors in all); not changed during therapy adherence assessment: not reported screening/titration phase: unclear	primary: flow-mediated dilatation HbA1c: yes hypoglycaemia: no glycaemic excursions: no total daily dose: no weight change: no complication rates: no adverse events: no health-related quality of life: no other: brachial artery reactivity; laboratory assessments, lipid profile timing of assessment: baseline, 4 months

Study	Design	Participants	Interventions	Outcome measures
		BMI: not reported ethnicity: not reported diabetes duration: not reported previous medication: not reported comorbidities: not reported subgroups: none		
Berhanu 2007 USA	focus: safety and efficacy of pioglitazone administered alone or in combination with metformin in reducing insulin dosage requirements for improved glycaemic control in patients with type 2 diabetes design: randomised, double-blind, placebo-controlled trial multi-centre duration: 20 weeks follow-up: no post-intervention follow-up funding: Takeda Global R&D Centre Risk of bias: ++	total number: 220 N PIO + ins: 110; 96 completed the trial N P + ins: 112; 102 completed the trial inclusion criteria: patients with documented type 2 diabetes; age 18-80 years; could self-monitor blood glucose; previous combination therapy failed (HbA1c ≥8.0%) ≤3 months before screening (combination therapy = sulphonylurea plus metformin, insulin plus metformin after failed sulphonylurea, or insulin alone after failed combination therapy with metformin and sulphonylurea (>50% maximum sulphonylurea and ≥2000 mg/day metformin required); C-peptide ≥0.7 ng/ml; FPG >120 mg/dL exclusion criteria: thiazolidinediones use <30 days or insulin treatment >30 months before screening; BMI <20 or >45 kg/m2; history of myocardial infarction, acute cardiovascular event, or cerebrovascular accident <6 months before screening; cardiac rhythm disturbance; significant cardiovascular disease including NYHA class III or IV; uncontrolled hypertension; LDL ≥175 mg/dL,	PIO + ins: pioglitazone titrated to 45 mg/day during first 4 weeks of treatment, plus insulin as below P + ins: identical placebo plus insulin as below both groups: all patients received one or multiple daily injections of Humalog, Humulin 70/30 or Humulin N; insulin adjusted to achieve FPG <140 mg/dL while avoiding hypoglycaemia co-interventions: excluded medications before and during study; hydrochlorothiazide (at doses >25 mg/day), glucocorticoids, steroid injections for joints, niacin; concurrent use of weight-loss agents and antidiabetic medications not included in the study were not permitted; patients maintained stable metformin and, as applicable, previous statin use for duration of study; 98.2% in both groups used metformin; 30.9% in pio group and 28.6% in placebo group used statins adherence assessment: pill counts (99.1 to 99.4% adherence) screening/titration phase: 1 week screening; instructions on insulin use and up to one week	primary: change in insulin dosage from baseline to study end HbA1c: yes hypoglycaemia: hypoglycaemic events (self-monitored blood glucose <60 mg/dL or laboratory value <70 mg/dL, more than two simultaneous hypoglycaemia symptoms relieved by oral glucose-containing substance, or resulting in needing assistance for simple tasks) glycaemic excursions: no total daily dose: yes weight change: weight complication rates: no adverse events: yes; clinical examinations; ECG; ALT health-related quality of life: no other: lipid parameters, C-peptide timing of assessment: visits every two weeks for the first month, once a month thereafter

Study	Design	Participants	Interventions	Outcome measures
		triglycerides >500 mg/dL; ALT >1.5 times upper limit of normal; diabetic nephropathy or anaemia age: PIO + ins: 52.9 SD11.33 years; P + ins: 52.5 SD11.07 years gender: PIO + ins: 56.4% female; P + ins: 58.9% female BMI: PIO + ins: 30.7 SD6.09 kg/m2; P + ins: 31.8 SD6.2 kg/m2 ethnicity: PIO + ins: Hispanic 50.0%, non-Hispanic white 34.9%, non-Hispanic black 12.7%, other 2.7%; P + ins: Hispanic 58.9%, non-Hispanic white 25.9%, non-Hispanic black 11.6%, other 3.6% diabetes duration: PIO + ins: 7.7 SD6.15 years; P + ins: 8.5 SD5.43 years previous medication: PIO + ins: sulphonylureas plus metformin 90.0%, insulin and metformin 8.2%, insulin only 1.8%; P + ins: sulphonylureas plus metformin 92.9%, insulin and metformin 5.4%, insulin only 1.8% comorbidities: not reported subgroups: none	sulphonylurea discontinuation as applicable; insulin initiated and titrated to achieve FPG <140 and >70 mg/dL for 4 additional weeks; after titration period, insulin type, dose and administration schedule were left to the discretion of the clinical investigator; during titration period, instructions regarding diabetes, hypoglycaemia, nutrition, exercise; patients were randomised if FPG <140 mg/dL achieved during titration	
Fernandez 2008 USA	focus: relationship between glycaemic control, vascular reactivity and inflammation in type 2 diabetes design: double-blind, placebo-controlled randomised controlled trial	total number: 30 N PIO + ins: 10 N P + ins: 10 N ramipril + ins: 10 (not considered here) inclusion criteria: adult Mexican-Americans with type 2 diabetes requiring insulin therapy (HbA1c >8.0% despite optimised oral	PIO + ins: pioglitazone 45 mg/day; started at 15 mg daily and then increased to 30 mg daily in week 2 and to 45 mg daily in week 4 P + ins: placebo ramipril + ins: ramipril 10 mg/day (not considered here) all groups: 3-day comprehensive diabetes education and nutritional	primary: vascular analyses HbA1c: yes hypoglycaemia: yes (symptomatic hypoglycaemia requiring glucose ingestion) glycaemic excursions: no total daily dose: yes weight change: yes complication rates: no

Study	Design	Participants	Interventions	Outcome measures
	single centre duration: 36 weeks follow-up: no post-intervention follow-up funding: American Diabetes Association, Takeda Pharmaceuticals Risk of bias: +	therapy); patients on insulin combination therapy with metformin, sulphonylureas or meglitinides included exclusion criteria: insulin combination therapy with thiazolidinediones age: mean age ~46 years (no details) gender: overall ~60% female (no details) BMI: overall ~31-33 kg/m2 (no details) ethnicity: Mexican-American diabetes duration: 6.2-8.4 years previous medication: use of oral antidiabetic medications similar between groups comorbidities: not reported subgroups: none	programme; patients could select between insulin therapy using multiple daily injections (basal-bolus therapy using combination of insulin glargine at bedtime plus premeal insulin aspart) or continuous subcutaneous infusion (Meditronic/Minimed or Animas pump using basal infusion and premeal boluses of insulin aspart); insulin dose adjusted to achieve the following glycaemic goals: fasting and pre-meal capillary blood glucose 80 – 120 mg/dL, 2-h post-meal glucose <160 mg/dL, bedtime glucose <140 mg/dL co-interventions: patients on ACE-inhibitors or angiotensin II receptor blockade were switched to alpha-methyl dopa (at least 2 months before study) and the dose adjusted to re-establish blood pressure control (<130/80 mmHg) before enrolment; other medication allowed if stable for at least 3 months; nearly half the patients were using a statin and one third was on antihypertensive therapy adherence assessment: compliance with treatment ascertained during each visit (no details) screening phase: no	adverse events: yes health-related quality of life: no other: euglycaemic-hyperinsulinaemic clamp; vascular studies; lipid parameters timing of assessment: clinic visits at 2- to 4-week intervals during first 3 months, every 2 months thereafter
Mattoo 2005 Worldwide	focus: effect of pioglitazone plus insulin versus placebo plus insulin on glycaemic control, serum lipid profile, and	total number: 289 N PIO + ins: 142; 128 completed the trial N P + ins: 147; 135 completed the trial	PIO + ins: 30 mg pioglitazone plus insulin P + ins: identical placebo plus insulin both: all patients received diabetes education, including dietary and	primary: change in HbA1c level from baseline to endpoint HbA1c: HbA1c hypoglycaemia: yes (1. subjective symptoms only, 2. subjective symptoms with

Study	Design	Participants	Interventions	Outcome measures
	selected cardiovascular risk factors in patients with type 2 diabetes whose disease was inadequately controlled with insulin therapy alone, despite efforts to intensify the treatment design: randomised double-blind, placebo-controlled parallel group trial multi-centre duration: 6 months follow-up: no post-intervention follow-up funding: Eli Lilly, Takeda Europe Risk of bias: ++	inclusion criteria: type 2 diabetes diagnosed according to WHO criteria, use of insulin therapy (with or without oral antihyperglycaemic medication) for ≥3 months, HbA1c ≥7.5% at screening, ≥30 years at diagnosis exclusion criteria: type 1 diabetes, clinical signs or symptoms of any chronic systemic condition (defined), signs or symptoms of drug or alcohol abuse; previous therapy with thiazolidinediones, systemic glucocorticoid therapy, nicotinic acid at >500 mg/d, or therapy for malignancy other than basal cell or squamous skin cancer; women breastfeeding or pregnant, women of childbearing potential without active birth control age: PIO + ins: 58.8 SD7.4 years; P + ins: 58.9 SD6.9 years gender: PIO + ins: 56.3% female; P + ins: 57.1% female BMI: PIO + ins: 32.5 SD4.8 kg/m2; P + ins: 31.8 SD5.0 kg/m2 ethnicity: not reported diabetes duration: PIO + ins: 163.4 SD81.0 months; P + ins: 160.9 SD73.7 months previous medication: 149 patients previously on oral agents (metformin n=109, sulphonylurea n=19, metformin plus sulphonylurea n=17, other n=4 comorbidities: not reported subgroups: none	exercise guidelines, and were instructed to maintain their individual diet and exercise regimens throughout the study; patient diaries for self-monitoring blood glucose; insulin dose reduced by 10% at randomisation to avoid hypoglycaemia and adjusted thereafter based on self-monitored blood glucose (SMGB) levels co-interventions: patients were allowed to use other medication as required, except another oral antidiabetic agent, systemic glucocorticoid therapy, or nicotinic acid (>500 mg/d) adherence assessment: capsule count (compliance rate ≥97.2%) screening phase: up to 14 days lead-in phase, patients remained on prescribed insulin therapy regimen, as monotherapy or with oral antihyperglycaemic agent; patients with HbA1c ≥7.5% then proceeded to insulin intensification period (3 months): insulin dose and number of injections adjusted to achieve fasting and preprandial blood glucose <5.5. mmol/L and 2-h postprandial blood glucose <7.5 mmol/L; patients with HbA1c ≥7.0% after insulin intensification were randomised to pioglitazone plus insulin or placebo plus insulin	SMBG ≥2.8 mmol/L, 3. subjective symptoms with SMBG <2.8 mmol/L, 4. SMBG <2.8 mmol/l without symptoms) glycaemic excursions: no total daily dose: yes weight change: yes complication rates: no adverse events: yes; adverse events, laboratory testing, physical examination health-related quality of life: no other: lipid parameters timing of assessment: 5 visits between randomisation and end of study
Raz 2005	focus: efficacy and	total number: 283	PIO + ins: 30 mg pioglitazone once	primary: end of trial HbA1c

Study	Design	Participants	Interventions	Outcome measures
Worldwide	safety of biphasic insulin aspart 30/70 (BIAsp 30) plus pioglitazone versus glibenclamide plus pioglitazone and BIAsp 30 monotherapy in type 2 diabetes design: randomised, open-label, parallel group trial multi-centre duration: 18 weeks follow-up: no post-intervention follow-up funding: Novo Nordisk Risk of bias: +	N PIO + ins: 93; 73 completed the trial N PIO + glibenclamide: 93; 56 completed the trial (not considered here) N ins mono: 97; 75 completed the trial inclusion criteria: male and female patients with type 2 diabetes; age ≥18 years; BMI ≤40 kg/m2; treatment with sulphonylurea (SU) (monotherapy or combination therapy) ≥3 months before screening; insufficient glycaemic control (HbA1c 7.4 – 14.7%) exclusion criteria: significant disease or conditions likely to affect trial or health outcomes (including history of drug or alcohol dependence, impaired hepatic function, cardiac disease) age: PIO + ins: 56.7 SD10.5 years; ins mono: 55.2 SD9.1 years gender: PIO + ins: 47% female; ins mono: 35% female BMI: PIO + ins: 29.4 SD4.6 kg/m2; ins mono: 29.5 SD4.9 kg/m2 ethnicity: not reported diabetes duration: PIO + ins: 9.2 SD5.3 years; ins mono: 10.0 SD5.8 years previous medication: patients taking other oral agents with SU: PIO + ins: none 14.0%, acarbose 9.7%, meglitinides 3.2%, metformin 83.9%, thiazolidinediones 7.5%; ins mono: none 13.4%, acarbose 12.4%, meglitinides 1.0%, metformin 80.4%, thiazolidinediones 4.1%	daily after breakfast plus biphasic insulin aspart 30/70 (BIAsp 30). BIAsp 30 initiated at a dose of 0.2 U/kg/day. PIO + glibenclamide: 30 mg pioglitazone once daily after breakfast plus glibenclamide (starting dose 5 mg in patients already on glibenclamide, equivalent dose not exceeding 10 mg in patients previously on other sulphonylureas) (not considered here) ins mono: BIAsp 30 initiated at a dose of 0.3 U/kg/day insulin therapy: biphasic insulin aspart 30/70 (30% rapid-acting soluble insulin aspart, 70% intermediate-acting protamine-crystallised insulin aspart); BIAsp 30 injected immediately (within 5 mins) before breakfast (50% of dose) and before dinner (50% of dose); BIAsp 30 titrated individually by patients using self-monitored blood glucose (SMBG) to achieve target blood glucose values of 5 to 8 mmol/L for fasting, preprandial and nighttime measurements, and 5 to 10 mmol/L for postprandial readings; BIAsp 30 injections with NovoPen 3; all dose titrations completed within 8 weeks of treatment co-interventions: any patient treated with insulin sensitiser other than pioglitazone was told to stop treatment 14 days before	HbA1c: yes hypoglycaemia: major hypoglycaemic episodes (patient unable to self-treat, blood glucose <50 mg/dL, or when symptoms remitted after administration of intravenous glucose or intramuscular glucagons after food intake); minor hypoglycaemic episodes (blood glucose <50 mg/dL, patient handled the event without assistance from others); symptomatic episodes (hypoglycaemic symptoms present but not confirmed by blood glucose measurement, assistance from others not required) glycaemic excursions: yes, blood glucose profiles (7 and 8 point) total daily dose: yes weight change: weight complication rates: no adverse events: yes health-related quality of life: no other: lipid profiles timing of assessment: screening, 8 weeks, end of trial (HbA1c); baseline, 4, 8, 12, 18 weeks (lipids)

Study	Design	Participants	Interventions	Outcome measures
		comorbidities: not reported subgroups: none	randomisation; no manipulation of lipid lowering regimens adherence assessment: checking patient diaries screening phase: none	
Rosenstock 2002 (pioglitazone 014 study group) USA	focus: effect of two doses of pioglitazone (15 or 30 mg) in combination with a stable insulin regimen to improve glycaemic control in patients whose type 2 diabetes is poorly controlled despite current insulin therapy design: double-blind, placebo-controlled randomised controlled trial multi-centre duration: 16 weeks follow-up: no post-intervention follow-up funding: Takeda Pharmaceuticals Risk of bias: +	total number: 566 N PIO15 + ins: 191; 161 completed the trial N PIO30 + ins: 188; 172 completed the trial N P + ins: 187; 164 completed the trial inclusion criteria: 30 to 75 years, type 2 diabetes; insulin treatment for ≥30 units/day for ≥months, with stable dosage for at least 30 days; at screening HbA1c ≥8.0%, fasting C-peptide >0.7 µg/L exclusion criteria: history of ketoacidosis, unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; impaired hepatic function (AST, ALT, total bilirubin or alkaline phosphatase >2.5 times upper limit of normal; impaired kidney function (serum creatinine >1.8 mg/dL); anaemia; unstable or symptomatic cardiovascular or cerebrovascular conditions (defined) age: PIO15 + ins: 56.9 SE10.4 years; PIO30 + ins: 57.5 SE9.9 years; P + ins: 56.7 SE9.4 years gender: PIO15 + ins: 53.9% female; PIO30 + ins: 49.5% female; P + ins: 54.5% female BMI: PIO15 + ins: 33.2 SE5.4 kg/m2; PIO30 + ins: 34.3 SE6.2 kg/m2; P +	N PIO15 + ins: 15 mg pioglitazone plus usual insulin regimen N PIO30 + ins: 30 mg pioglitazone plus usual insulin regimen N P + ins: placebo plus usual insulin regimen all: insulin dose could be decreased in response to hypoglycaemia; maximum permitted decrease in insulin dose at any one time: 10% of patient's current total daily dosage; reduced dose remained fixed unless new occurrences of hypoglycaemia warranted another 10% decrease co-interventions: lipid-lowering medications allowed, provided patient had been taking stable dose for >60 days and regimen was continued without alteration throughout the study; no dietary intervention / modification adherence assessment: no screening phase: 2 weeks; patients on oral antihyperglycaemic agent in addition to insulin discontinued oral agent at beginning of screening period; screening followed by one week (for patients on stable insulin monotherapy) or four weeks (for patients previously on insulin plus oral agents) single-blind placebo	primary: unclear, presumably HbA1c at study endpoint HbA1c: yes hypoglycaemia: yes; defined as FPG ≤100 mg/dL (5.6 mmol/L), symptoms of hypoglycaemia not explained by other conditions glycaemic excursions: no total daily dose: yes weight change: yes complication rates: no adverse events: yes; laboratory values, vital signs, ECGs, any adverse events health-related quality of life: no other: serum lipid measurements (triglycerides and cholesterol) timing of assessment: patients seen every four weeks

Study	Design	Participants	Interventions	Outcome measures
		ins: 33.2 SE5.2 kg/m2 ethnicity: PIO15 + ins: 74.9% Caucasian; PIO30 + ins: 73.4% Caucasian; P + ins: 71.1% Caucasian diabetes duration: not reported previous medication: 88% insulin monotherapy; 12% combination with oral agents (8% metformin, 2% glyburide, 2% glipizide); 134 patients receiving serum lipid reducing agent (classes approximately evenly distributed across groups) comorbidities: not reported subgroups: none	treatment period (stable insulin regimen in combination with placebo)	
Scheen 2006 19 European countries part of PROactive trial (investigating only patients concomitantly treated with insulin) abstract only	focus: effects of pioglitazone on the secondary prevention of macrovascular events in type 2 diabees design: randomised double-blind outcome study multi-centre duration: mean 34.5 months follow-up: no post-intervention follow-up funding: Takeda Europe, Eli Lilly Risk of bias: +	total number: 1760 N PIO + ins: 864 N P + ins: 896 inclusion criteria: male or female with type 2 diabetes; age 35 to 75 years; HbA1c level above the upper limit of normal (local equivalent of 6.5% for a Diabetes Control and Complications Trial-traceabel assay), despite management of diabetes with diet alone or with oral blood glucose lowering agents; increased risk of macrovascular disease as defined in the trial; insulin allowed if given in combination with oral agents exclusion criteria: current use of pioglitazone or any other thiazolidinediones; signs of type 1 diabetes; insulin as sole therapy for diabetes; planned revascularisation; symptomatic heart failure; leg ulcers, gangrene, or pain at rest; haemodialysis; significantly impaired	PIO + ins: pioglitazone plus previous treatment; forced titration phase in the first two months of treatment with stepwise increase of pioglitazone dose from 15 mg to 30 mg and then up to 45 mg, to maintain patients at maximum tolerated dose; dose could be adjusted at any time within 15 mg to 45 mg range based on tolerability P + ins: placebo plus previous treatment both: investigators encouraged to maintain glycaemia at <6.5% co-interventions: proportion of concomitant oral therapy remained similar: PIO + ins: metformin alone 47%, sulphonylurea alone 16%, metformin plus sulphonylurea 10%; P + ins: metformin alone 52%, sulphonylurea alone 16%, metformin plus sulphonylurea 11% adherence assessment: no	primary: (of PROactive trial) time from randomisation to any of (composite endpoint): all-cause mortality, non-fatal myocardial infarction, acute coronary syndrome, cardiac intervention (including coronary artery bypass graft or percutaneous coronary intervention), stroke, major leg amputation (above ankle), bypass surgery; or revascularisation in the leg HbA1c: yes hypoglycaemia: yes (but undefined) glycaemic excursions: no total daily dose: yes weight change: no complication rates: not reported here adverse events: yes health-related quality of life: no

Study	Design	Participants	Interventions	Outcome measures
		hepatic function (serum alanine aminotransferase >2.5 times upper limit of normal) age: not reported for subgroup on insulin therapy gender: not reported for subgroup on insulin therapy BMI: not reported for subgroup on insulin therapy ethnicity: not reported for subgroup on insulin therapy diabetes duration: not reported for subgroup on insulin therapy previous medication: at baseline, insulin combined with metformin monotherapy in 53%, sulphonylurea monotherapy in 24%, dual therapy with metformin and sulphonylurea 12% comorbidities: not reported subgroups: abstract reports subgroup of larger trial – in the main trial only about one third of patients received concomitant insulin therapy	screening phase: not reported	other: none (in this abstract) timing of assessment: unclear
Shah 2007 USA abstract only	focus: effects of a pioglitazone and insulin combination versus insulin therapy alone on body fat distribution design: randomised double-blind placebo-controlled trial single centre duration: 12 to 16 weeks	total number: 25 N PIO + ins: 12 N P + ins: 13 inclusion criteria: insulin-treated, obese type 2 diabetes patients exclusion criteria: not reported age: not reported gender: not reported BMI: 36.5 kg/m2 ethnicity: not reported diabetes duration: not reported	PIO + ins: pioglitazone (30 mg titrated to 45 mg) and insulin P + ins: placebo and insulin co-interventions: not reported adherence assessment: not reported	primary: body fat distribution HbA1c: HbA1c hypoglycaemia: no glycaemic excursions: no total daily dose: no weight change: yes complication rates: no adverse events: no health-related quality of life: no other: subcutaneous adipose tissue, visceral adipose tissue

Study	Design	Participants	Interventions	Outcome measures
	follow-up: no post-intervention follow-up setting: unclear funding: not stated Risk of bias: -	previous medication: not reported comorbidities: not reported subgroups: none		(abdominal CT scans) timing of assessment: not reported

Quality assessment of studies

Study	Method of randomisation	Allocation concealment	Blinding	Intention to treat data analysis	Percentage who completed trial	Power calculation	Similarity of groups at baseline	Sponsorship/author affiliation
Asnani 2006	carried out by research pharmacist using predetermined randomisation code	yes	double-blind	not reported	PIO + ins: 80% P + ins: 80%	yes	yes	Takeda, NIH
Berhanu 2007	computer-generated schedule	yes	double-blind	yes	PIO + ins: 87.3% P + ins: 91.1%	yes	stated that placebo group had slightly higher BMI and longer diabetes duration, but no p-values given	Takeda Global R&D Centre
Fernandez 2008	not reported	not reported	double-blind	not reported	unclear – all?	yes (on vascular parameters)	yes	American Diabetes Association, Takeda Pharmaceuticals
Mattoo 2005	central randomisation table administered by an automated interactive voice	yes	double-blind	yes	PIO + ins: 90% P + ins: 92%	yes	yes	Eli Lilly, Takeda Europe

Study	Method of randomisation	Allocation concealment	Blinding	Intention to treat data analysis	Percentage who completed trial	Power calculation	Similarity of groups at baseline	Sponsorship/author affiliation
	system							
Raz 2005	unclear ("assignment of lowest available patient number")	not reported	no	yes	PIO + ins: 78% ins mono: 77%	yes	yes	Novo Nordisk
Rosenstock 2002	not reported	not reported	double-blind	yes	PIO15 + ins: 84% PIO30 + ins: 91% P + ins: 88%	not reported	yes	Takeda Pharmaceuticals
Scheen 2006	central interactive voice-response system	not reported	double-blind	yes	not reported	yes	not reported	Takeda Europe, Eli Lilly
Shah 2007	not reported	not reported	double-blind	not reported	not reported	not reported – small numbers, probably underpowered	not reported	not reported

Results by study

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
HbA1c					
Asnani 2006	HbA1c (%)	PIO + ins: 10.0 SD2.3% P + ins: 8.7 SD2.3%	PIO + ins: 8.4 SD2.0% P + ins: 8.6 SD1.4%		p not reported (p<0.05 for pio before and after)
Berhanu 2007	HbA1c (%)	PIO + ins: 8.4 SD0.13% P + ins: 8.6	PIO + ins: 6.81% P + ins: 7.23%	PIO + ins: -1.6 SD0.11% P + ins: -1.4 SD0.11 %	p=NS

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
		SD0.13%			
Fernandez 2008	HbA1c (%)	PIO + ins: 9.0 SD0.7% P + ins: 9.2 SD0.4%	PIO + ins: 6.9 SD0.3% P + ins: 7.2 SD0.1%		
Mattoo 2005	HbA1c (%)	PIO + ins: 8.85 SE0.11% P + ins: 8.79 SE0.1%	PIO + ins: 8.11 SE0.09% P + ins: 8.66 SE0.08%	difference between groups -0.55 SE0.1%	p<0.002
	percentage attaining HbA1c <7.0%		PIO + ins: 18% P + ins: 6.9%		
	HbA1c subgroups: patients using ≤2 or ≥3 insulin injections				no significant difference
	HbA1c subgroups: previous use of oral antidiabetic agents			previous use of oral agents: PIO + ins: -0.90 SE0.14% P + ins: -0.11 SE0.13% no previous use of oral agents: PIO + ins: -0.65 SE0.11% P + ins: -0.2 SE0.12%	no significant difference for subgroups
Raz 2005	HbA1c (%)	PIO + ins: 9.6 SD1.3% ins mono: 9.5 SD1.3%	PIO + ins: 8.4 SD1.2% ins mono: 9.0 SD1.3%		p=0.008
Rosenstock 2002	HbA1c (%)	PIO15 + ins: 9.75 SE0.1% PIO30 + ins: 9.84 SE0.1% P + ins : 9.75		PIO15 + ins: -0.99 SE0.08% PIO30 + ins : -1.26 SE0.08% P + ins : -0.26 SE0.08%	p<0.01 pioglitazone versus placebo

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
		SE0.1%			
Shah 2007	HbA1c (%)	PIO + ins : 7.6% P + ins : 7.8%	PIO + ins : 7.1% P + ins : 7.2%		p not reported, presumably non-significant
Scheen 2006	HbA1c (%)	PIO + ins: 8.4% P + ins: 8.5%	PIO + ins: 7.47% P + ins: 8.05%	PIO + ins: -0.93% P + ins: -0.45%	p<0.0001
hypoglycaemia					
Berhanu 2007	patients with hypoglycaemic events		PIO + ins: 46% (91% mild) P + ins: 31% (66% mild)		p<0.005
	severe hypoglycaemia (episodes)		PIO + ins: n=0 P + ins: n=4		p not reported
Fernandez 2008	patients with hypoglycaemic episodes		PIO + ins: n=4 P + ins: n=6		
Mattoo 2005	patients with subjective hypoglycaemic episodes		PIO + ins: 63.4% P + ins: 51.0%		p<0.05
	clinical hypoglycaemic episodes (blood glucose <2.8 mmol/L)				no significant difference
Raz 2005	major hypoglycaemic episodes		none		
	minor hypoglycaemic episodes (% patients)		PIO + ins: 12% ins mono: 15%		p not reported
	minor hypoglycaemic episodes (episodes)		PIO + ins: 15 ins mono: 47		p not reported
	symptoms only (% patients)		PIO + ins: 34% ins mono: 40%		p not reported
	symptoms only		PIO + ins: 115		p not reported

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
	(episodes)		ins mono: 171		
	incidence (per patient-week for all episodes)		PIO + ins: 0.083 ins mono: 0.132		p<0.05
	nocturnal hypoglycaemia (episodes)		PIO + ins: 0 ins mono: 8		p not reported
Rosenstock 2002	hypoglycaemia		PIO15 + ins: 8% PIO30 + ins: 15% P + ins: 5% (all considered mild to moderate)		
Scheen 2006	hypoglycaemia (not specified further)		PIO + ins: 41% P + ins: 29%		p<0.0001
glycaemic excursions					
Raz 2005					measurements before dinner, 90 mins after dinner, and at bedtime significantly lower in PIO + ins group than in ins monotherapy group
total daily dose					
Berhanu 2007	daily insulin dose	PIO + ins: 55.8 SD2.95 units P + ins: 57.7 SD2.95 units		PIO + ins: -12.0 SD1.84 units P + ins: +0.8 SD1.84 units adjusted mean difference between groups -12.5 units (95% CI: -17.5, -8.0)	p<0.001
Fernandez 2008	daily insulin dose	all groups: ~1.2 U/kg/day	PIO + ins: 1.0 U/kg/day P + ins: ~1.2		p not reported

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
			U/kg/day		
Mattoo 2005	daily insulin dose	PIO + ins: 0.96 SE0.03 U/kg/day P + ins: 0.92 SE0.03 U/kg/day	PIO + ins: 0.76 SE0.02 U/kg/day P + ins: 0.94 SE0.02 U/kg/day	difference between groups -0.18 SE0.02 U/kg/day	p<0.002
Raz 2005	daily insulin dose	PIO + ins: 0.2 U/kg/day ins mono: 0.3 U/kg/day	PIO + ins: 0.5 U/kg/day ins mono: 0.7 U/kg/day	PIO + ins: +0.3 U/kg/day ins mono: +0.4 U/kg/day	p=0.002
Rosenstock 2002	daily insulin dose	PIO15 + ins: 70.2 SE34.0 U/day PIO30 + ins: 72.3 SE38.5 U/day P + ins : 70.7 SE33.5 U/day	PIO15 + ins: 67.3 SE33.5 U/day PIO30 + ins: 64.2 SE32.7 U/day P + ins : 70.1 SE33.9 U/day		p not reported
Scheen 2006	daily insulin dose	PIO + ins: 47 U/day P + ins: 47 U/day	PIO + ins: 42 U/day P + ins: 55 U/day		p<0.0001; at final visit, insulin discontinued in 9% of pioglitazone group and 2% of placebo group (p<0.0001)
weight change					
Berhanu 2007	weight (kg)			PIO + ins: +4.39 kg P + ins: +2.42 kg	p not reported
	patients reporting weight gain			PIO + ins: n=10 P + ins: n=3	p not reported
Fernandez 2008	weight (kg)			PIO + ins: +4.4 kg P + ins: +1.7 kg	p not reported
Mattoo 2005	weight (kg)			PIO + ins: +4.05 SE4.03 kg	p not reported

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
				P + ins: +0.20 SE2.92 kg	
Raz 2005	weight (kg)			PIO + ins: +4.0 kg ins mono: +2.2 kg	p not reported
	patients experiencing weight gain (%)			PIO + ins: 8% ins mono: 2%	p not reported
Rosenstock 2002	weight (kg)	PIO15 + ins: 95.4 SE17.6 kg PIO30 + ins: 98.7 SE17.7 kg P + ins : 95.4 SE17.0 kg		PIO15 + ins: +2.3 kg PIO30 + ins: +3.7 kg P + ins : -0.04 kg	p not reported; weight gain related to decreases in HbA1c, p=0.002
Shah 2007	weight (kg)	PIO + ins: 107.1 kg P + ins: 108.7 kg	PIO + ins: 112.0 kg P + ins: 110.1 kg		p not reported, presumably non-significant
complication rates					
Berhanu 2007	cardiac events			PIO + ins: 5.5% P + ins: 10.7% (mostly ECG abnormalities)	p not reported
	deaths			no deaths	
lipid parameters					
Berhanu 2007	total cholesterol (mg/dL)	PIO + ins : 178 SD3.53 mg/dL P + ins : 183 SD3.6 mg/dL		PIO + ins: +5.7 SD2.75 mg/dL P + ins: +4.7 SD2.78 mg/dL	p=NS
	HDL cholesterol (mg/dL)	PIO + ins : 44.6 SD1.3 mg/dL P + ins : 42 SD1.3 mg/dL		PIO + ins: +4.3 SD0.75 mg/dL P + ins: -0.2 SD0.77 mg/dL	p<0.001

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
	LDL cholesterol (mg/dL)	PIO + ins : 107 SD3.1 mg/dL P + ins : 111 SD3.2 mg/dL		PIO + ins: +4.0 SD2.37 mg/dL P + ins: +0.9 SD2.37 mg/dL	p=NS
	triglycerides (mg/dL)	PIO + ins : 123 SD7.5 mg/dL P + ins : 141 SD7.6 mg/dL		PIO + ins: -0.2 SD9.80 mg/dL P + ins: +43.7 SD9.96 mg/dL	p<0.001
Fernandez 2008	total cholesterol (mg/dL)	PIO + ins : 176 SD9 mg/dL P + ins : 195 SD9 mg/dL	PIO + ins : 175 SD16 mg/dL P + ins : 180 SD8 mg/dL		p=NS
	LDL cholesterol (mg/dL)	PIO + ins: 107 SD5 mg/dL P + ins: 121 SD8 mg/dL	PIO + ins: 105 SD12 mg/dL P + ins: 115 SD7 mg/dL		p=NS
	HDL cholesterol (mg/dL)	PIO + ins: 45 SD3 mg/dL P + ins: 49 SD4 mg/dL	PIO + ins: 51 SD3 mg/dL P + ins: 46 SD3 mg/dL		p<0.05 pioglitazone versus baseline
	VLDL cholesterol (mg/dL)	PIO + ins: 109 SD16 mg/dL P + ins: 113 SD24 mg/dL	PIO + ins: 88 SD15 mg/dL P + ins: 93 SD19 mg/dL		
	triglycerides (mg/dL)	PIO + ins: 148 SD17 mg/dL P + ins: 146 SD15 mg/dL	PIO + ins: 123 SD11 mg/dL P + ins: 132 SD18 mg/dL		p<0.05 pioglitazone versus baseline
Mattoo 2005	HDL cholesterol (mmol/L)	PIO + ins : 1.23 SE0.03 mmol/L P + ins : 1.24 SE0.03 mmol/L	PIO + ins : 1.35 SE0.02 mmol/L P + ins : 1.21 SE0.02 mmol/L	difference between groups 0.13 SE0.03 mmol/L	p<0.002

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
	LDL cholesterol (mmol/L)	PIO + ins : 3.20 SE0.09 mmol/L P + ins : 3.18 SE0.08 mmol/L	PIO + ins : 3.18 SE0.06 mmol/L P + ins : 3.10 SE0.06 mmol/L		p=NS
Raz 2005	triglycerides (mg/dL)		PIO + ins: 149 SD88 mg/dL ins mono: 158 SD88 mg/dL		p=NS
	total cholesterol (mg/dL)		PIO + ins: 212 mg/dL ins mono: 204 mg/dL		p=NS
	HDL cholesterol (mg/L)			difference between PIO + ins versus ins mono +4 SD1 mg/dL	p<0.01
	LDL cholesterol (mg/L)			no data shown	p=NS
Rosenstock 2002	triglycerides (mmol/L)	PIO15 + ins : 2.61 SE0.2 mmol/L PIO30 + ins : 2.96 SE0.2 mmol/L P + ins : 2.74 SE0.2 mmol/L		PIO15 + ins : +5.35 SE6.56% PIO30 + ins : -10.35 SE6.54% P + ins : +13.30 SE6.63%	p<0.05 PIO30 versus placebo
	HDL cholesterol (mg/dL)	PIO15 + ins : 43.42 SE0.95 mg/dL PIO30 + ins : 42.71 SE0.94 mg/dL P + ins : 42.66 SE0.96 mg/dL		PIO15 + ins : +7.07 SE1.58% PIO30 + ins : +9.13 SE1.57% P + ins : -0.21 SE1.59%	p<0.05 PIO30 versus placebo
	total cholesterol (mg/dL)	PIO15 + ins : 213.08 SE3.57 mg/dL		PIO15 + ins : +1.40 SE1.06% PIO30 + ins : +0.40	p=NS

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
		PIO30 + ins : 207.32 SE3.53mg/dL P + ins : 214.03 SE3.58 mg/dL		SE1.05% P + ins : -0.66 SE1.07%	
	LDL cholesterol (mg/dL)	PIO15 + ins : 127.33 SE3.07 mg/dL PIO30 + ins : 121.69 SE3.06mg/dL P + ins : 130.95 SE3.05 mg/dL		PIO15 + ins: +2.83 SE1.80% PIO30 + ins: +5.05 SE1.71% P + ins : -1.41 SE1.74%	p=NS
adverse events					
Berhanu 2007	oedema			PIO + ins: n=10 P + ins: n=5 (all mild to moderate)	p not reported
	serious adverse events			PIO + ins: n=4 P + ins: n=2 (none considered to be related to study medication)	p not reported
Mattoo 2005	withdrawal due to adverse events			PIO + ins: n=7 P + ins: n=3	p not reported
	oedema			PIO + ins: n=20 (10 classified as mild) P + ins: n=5 (3 classified as mild)	p not reported
Raz 2005	withdrawal due to adverse events			PIO + ins: n=1 ins mono: n=2	p not reported
	patients with product-related adverse events			PIO + ins: 28% ins mono: 20%	p not reported

Study	Outcome	Baseline	End of study	Change from baseline / difference between groups	p value (between groups)
	peripheral oedema			PIO + ins: 6% ins mono: 0	p not reported
	serious adverse events			PIO + ins: n=0 ins mono: n=2 (none considered to be related to study medication)	
Rosenstock 2002	withdrawal due to adverse events			PIO15 + ins: 1.6% PIO30 + ins: 2.6% P + ins : 3.2%	p not reported
	oedema			PIO15 + ins: 12.6% PIO30 + ins: 17.6% P + ins : 7.0%	p not reported
	cardiovascular adverse events			PIO15 + ins and PIO30 + ins: 7.9% P + ins : 7.0%	p=NS; none considered related to study medication
Scheen 2006	oedema			PIO + ins: 31% P + ins: 18%	p<0.0001
HR QoL	not reported				